Pediatrics

VOLUME 6 AUGUST 1950 NUMBER 2

ORIGINAL ARTICLES

ERYTHROBLASTOSIS FETALIS

I. Problems in the Interpretation of Changing Mortality in Erythroblastosis Fetalis

By VICTOR C. VAUGHAN III, M.D., FRED H. ALLEN, JR., M.D., AND LOUIS K. DIAMOND, M.D.
Boston

SINCE the demonstration[1] almost a decade ago that erythroblastosis fetalis was associated with sensitization of the Rh-negative mother to the red blood cells of her Rh-positive infant, three major modifications of treatment have been made in the clinical management of such infants. It was first proposed[2] that rational management of sick infants might demand that they be transfused with Rh-negative rather than Rh-positive blood. Early induction of labor in the sensitized mother was later proposed[3] in the hope of sparing the infant a more severe illness dependent upon prolonged intra-uterine existence. Lastly, the technic of exchange transfusion, a theoretically reasonable procedure, has been developed to the point where it is entirely practical, and early reports of its use[4, 5] are very optimistic in presenting the results achieved.

It is the purpose of this paper to show that there are serious handicaps to the accurate assay of these therapeutic measures in two groups of cases of erythroblastosis fetalis at the authors' disposal. With the introduction of each new measure, there have occurred changes in the nature of the clinical material being treated, and observed changes in overall mortality figures have been found to depend largely on factors other than the inherent

From the Department of Pediatrics, Harvard Medical School, the Children's Medical Center, the Boston Lying-in Hospital, and the Blood Grouping Laboratory, Boston.

Aided by a grant from the United States Public Health Service. Support of the Blood Bank of the Children's Hospital from the Variety Club of Boston has been most helpful in caring for these patients.

Presented in part at the Annual Meeting of the Society for Pediatric Research, Atlantic City, May 1949.

(Received for publication Dec. 4, 1949.)

therapeutic value of any measure adopted. This report presents the results of a 12 year survey of 539 cases of erythroblastosis fetalis seen by a single group at the Children's Hospital, Boston, and the Boston Lying-in Hospital. It will be apparent that the case material of the Boston Lying-in Hospital is very different from that at the Children's Hospital and accordingly the two bodies of clinical material will be considered separately.

The authors have elected for this analysis to consider the clinical course of erythroblastosis fetalis as having five possible outcomes: (a) stillbirth of the fetus, with or without hydrops fetalis, (b) death in a live born infant without there being clinical or pathologic signs of kernicterus, (c) kernicterus in a live born infant, with or without survival of the acute phase of the illness, (d) complete recovery from an illness of whatever severity which is recognized as erythroblastosis fetalis, and (e) recovery without clinical evidence of disease in the Rh-positive infant of an Rh-negative mother in whom Rh antibodies have been demonstrated at the time of delivery. About one third of the cases of kernicterus in this series have survived the neonatal period, always with residual brain damage. They make up about 5% of the surviving cases of erythroblastosis fetalis. The cases of surviving kernicterus have not been separated from fatal kernicterus in preparing the tables, since it is the authors' strong feeling that kernicterus, whether surviving or not, must be viewed as a unitary problem. While it will be shown, for example, in reports to follow that kernicterus bears little relationship to other causes of death in erythroblastosis fetalis, there is no evidence that there is any qualitative difference between those cases of kernicterus which survive and those which do not. Quantitative differences may well exist.

It has been possible generally to recognize those offspring who show no clinical illness in spite of maternal sensitization only since the introduction of the slide test[6] into the diagnostic repertory. Prior to 1944 only mothers with potent anti-Rh agglutinins active in a saline medium were likely to be recognized as sensitized. These mothers are generally in the minority. The use of serum and albumin as suspending media[7] for the Rh testing has increased the ease with which the diagnosis of sensitization of the Rh-negative woman can be made.

Mortality of Erythroblastosis Fetalis at the Children's Hospital

Table 1 summarizes 12 years' experience with 349 cases of erythroblastosis fetalis at the Children's Hospital. Included are four years (1937-1940) just preceding the discovery

TABLE 1

Relation of Outcome to Age on Admission
(Children's Hospital, 1937–1948)

Age on admission	1937–1940		1941–1944		1945–1946		1947–1948	
	P	M	P	M	P	M	P	M
24 hr. or less	6	67%	11	64%	20	60%	91	19%
24 hr. to 7 days	6	33%	61	33%	37	35%	22	23%
Over 7 days	18	28%	30	13%	23	9%	15	0
Unknown (less than 48 hr.)					4	100%	5	40%
Totals	30	37%	102	30%	84	37%	133	18%

P = no. of patients.
M = mortality, including surviving cases of kernicterus (see text).

of the Rh factor, four years (1941-1944) during which the presumptive diagnosis of erythroblastosis could sometimes be confirmed by examination of the blood of patient and mother but sometimes not, and, lastly, four years (1945-1948) during which it has been generally possible to prove by laboratory tests the sensitization of the mother before delivery and to anticipate an illness in the newborn infant.

The years 1945-1948 are divided into a two year period (1945-1946) in which exchange transfusion was not available, and a two year period (1947-1948) during which exchange transfusion has generally been available for babies admitted to the Children's Hospital within the first 24 hours of life.

The arbitrary division of the clinical material into three groups, according to the age at time of admission to the hospital, brings out several important features (table 1). First, the most obvious effect of the discovery of the Rh factor (1940) was not a lowering in the mortality of erythroblastosis fetalis, but a tendency for patients to be admitted earlier in the course of the disease and in increasing numbers. For six years after discovery of the Rh factor the case mortality* remained over 60% in infants in whom the rapid development of clinical signs of erythroblastosis fetalis led to transfer to the Children's Hospital for treatment within the first 24 hours of life. The case mortality among infants admitted later in the first week remained about 35% during this same period. Secondly, babies admitted after the first week of life have in all years had a good prognosis, if kernicterus were not present on admission. Of the 11 patients admitted after seven days who failed to recover completely, 9 had developed kernicterus during the first week of life. Two patients were admitted moribund with anemia during the second week of life, and presumably might have been saved if admission had occurred earlier. The 7% decrease in over-all mortality (cf. footnote) which occurred between the 1937-1940 period and the 1941-1944 period took place entirely within the group of infants admitted after the first week of life. Since a bad result in such infants was generally determined by the onset of kernicterus before entry, the outcome has not depended on methods of therapy except so far as simple correction of anemia has been concerned. In the babies admitted during the first week of life there is seen no difference in mortality, which suggests that the change in 1941 from the general use of untyped blood (usually Rh-positive) to the use of Rh-negative blood in therapy did not result in a generally lowered mortality. This is in accord with the experience of those who have carefully studied other series of cases.[8-11]

When the results in 1947-1948 are compared with former years, it is seen at once that there has been not only a profound change in the nature of the clinical material so far as age at time of admission to the hospital is concerned, but also a concomitant and highly significant (by χ^2) change in mortality of erythroblastosis fetalis, particularly in those patients admitted during the first day of life. It cannot be assumed, however, that this fall in mortality rate was due entirely to the lifesaving properties of exchange transfusion. First, the great dislocation of patients (according to time of admission) into the group admitted on the first day has occurred at the expense of the groups admitted in former years only after two or three days. Accordingly, infants are now admitted early who, with the same illness in other years, would have been admitted later in the course of the disease, and these infants bring an inherently better prognosis to the group of infants now admitted on the first day.

Also, in the period 1947-1948 many of the babies admitted on the first day (usually the

* The term "mortality" has in this paper been extended to include all bad results, and includes all cases of kernicterus, whether or not they died, as discussed above.

first Rh-positive infant born to the mother after sensitization is detected) were admitted not for clinical erythroblastosis fetalis, as was always the case before the advent of exchange transfusion, but without clinical signs in anticipation of illness because the mother was known to be Rh-negative and sensitized. The results of the survey of the Boston Lying-in Hospital case material (see below) indicate that as many as 15-20% of these patients admitted to the Children's Hospital on the first day of life during the years 1947-1948 would likely have had no illness (jaundice or anemia) of such severity as to be recognized as erythroblastosis fetalis. These babies would not have been transferred to the Children's Hospital if possible need for exchange transfusion had not been anticipated on the basis of demonstrated maternal sensitization during pregnancy. Accordingly it seems quite clear that the mortality since 1946 cannot be compared to previous years as far as evaluation of treatment is concerned, since the clinical material is not comparable in the two periods.

To complicate further the interpretation of the change in mortality during the years 1947-1948, the observation was made that even in the group of infants admitted after the first day but during the first week, where the mortality of bygone years was 35%, a fall in mortality to 23% has occurred. This is no direct result of exchange transfusion, since this procedure was not used in infants over 24 hours old during 1947 and 1948.

Finally, it should be made quite clear that if exchange transfusion of a normal-appearing, though potentially sick infant, or of a more seriously ill infant with erythroblastosis fetalis, has been done within the first few hours of life, there are no criteria whatsoever which allow one to make an accurate appraisal of what the untreated course of the disease might have been, especially if the outcome is favorable. It is believed that failure to appreciate this fact has led to interpretations of the results of exchange transfusion therapy[5] which rest on entirely untenable grounds.

In summary, during 12 years' time two noteworthy changes have been observed in the nature of the clinical material presented at the Children's Hospital for treatment of erythroblastosis fetalis. The first occurred at the time of the discovery of the Rh factor (1941) and consisted of increased numbers of admissions for erythroblastosis fetalis and a change in time of admission from predominantly after the first week of life to predominantly within the first week, though after the first day. There was no significant alteration in mortality. The second change took place early in 1947 after exchange transfusion became available, and consisted of a shift from admission predominantly after the first day of life to admission within the first day of life, often without clinical disease being manifest. There was a concomitant highly significant improvement in the apparent recovery rate of erythroblastosis fetalis, the interpretation of which is impossible in terms of simple therapeutic value of exchange transfusion, as previously explained.

Erythroblastosis Fetalis at the Boston Lying-In Hospital

Table 2 summarizes 12 years' experience with 200 cases of erythroblastosis fetalis seen at the Boston Lying-in Hospital. The four year periods, 1937-1940 and 1941-1944, and the two year periods, 1945-1946 and 1947-1948, have the same meaning here as above so far as developments in the field of study and treatment of erythroblastosis fetalis are concerned. However, the clinical material studied differs in an important respect from that at the Children's Hospital, namely, that the patients comprise all Rh positive offspring, including stillbirths, of Rh-negative sensitized mothers attending the clinic, whether the incompatibility is determined on clinical grounds alone (1937-1940), on clinical grounds

supplemented by Rh typing (1941-1944), or on serologic grounds only (since 1945). It is seen that since 1945 it has been recognized that many Rh-positive offspring of Rh-negative sensitized mothers have no clinical disease or such mild illness as to be within the limits of newborn variability. These babies are seen to comprise 18% of all cases of erythroblastosis fetalis seen since 1945, and 24% of the live born infants.

Table 2 gives the observed over-all mortality of erythroblastosis fetalis in live born infants from 1937-1940 as 35%, from 1941-1944 as 38%, from 1945-1946 as 34%, and from 1947-1948 as 20%. The figures for the first two 4 year periods are manifestly not comparable to the later periods, since there should have been 10 or more Rh-positive

TABLE 2

OUTCOME OF ERYTHROBLASTOSIS FETALIS
(Boston Lying-in Hospital, 1937–1948)

Outcome	1937–1940	1941–1944	1945–1946	1947–1948
No clinical disease			11	11
Recovered	11	21	20	24
Died, no kernicterus	3	3	7	3
Kernicterus	3	10	9	6
Stillborn	11	15	15	17
Totals	28	49	62	61
Mortality in live born	35%	38%	34%	20%

infants in each period who, though born to sensitized Rh-negative mothers, showed no clinical illness. There were probably also a few infants in the period 1937-1940 whose clinical illness was interpreted as icterus neonatorum, sepsis, asphyxia or toxic hepatitis, because of less adequate means of diagnosis. In any case, there is no change in mortality between the 1937-1940 and 1941-1944 groups of infants to indicate that the change in 1941 to the general use of Rh-negative blood in therapy was of any fundamental benefit.

Although the cases from the Boston Lying-in Hospital include all sensitized Rh-negative mothers in a large obstetric clinic, they do not represent from year to year a true cross-section of the community so far as Rh problems are concerned. Many mothers in late years have attended this clinic because its special interest in Rh problems is widely known both to referring physicians and to laymen in the community. In adjusting the data for this factor, the authors have considered as a referred case any woman who had her first erythroblastotic infant in another hospital. Table 3 shows that the number of referred cases has increased since 1940 from about 20% to about 40% of the clinic load of sensitized mothers. The result of this, as seen in table 4, has mainly been an increased number of stillborn infants with erythroblastosis fetalis, but not a significant change in the over-all prognosis for live born infants if the fact is taken into account that in referred cases there is a past history of erythroblastosis fetalis. The mortality in live born infants of referred mothers is high, but it is not significantly different from the outcome in the group of not-referred mothers who have had previous erythroblastotic infants, though there is a tendency to milder illness in the latter group. The contrast between both these groups and the group of infants of mothers who have not had previous erythroblastotic infants is striking, and will be dealt with more fully later. In any case, these data give no reason to feel that a failure to observe a change in mortality in live born

infants over the years is a reflection of the increased numbers of referred cases.

The introduction of exchange transfusion, which in 1947 so profoundly altered the nature of the clinical material at the Children's Hospital, has had no such effect at the Boston Lying-in Hospital. There has been a continued slight increase in the proportion of referred cases in the clinic, without this having any important bearing on mortality in live born infants. The over-all mortality in live born infants was 33% in 1945-1946 and 20% in 1947-1948 (table 2). This trend to better results in the last two year period has been observed both in the group of patients where there has been no previous infant with

TABLE 3

PERCENTAGE OF REFERRED CASES

(Boston Lying-in Hospital, 1937–1948)

	1937–1940	1941–1944	1945–1946	1947–1948
Total cases	28	49	62	61
Referred	5	9	18	25
% referred	18%	19%	29%	41%

TABLE 4

RELATION OF OUTCOME TO MATERNAL HISTORY AND REFERRAL

(Boston Lying-in Hospital, 1945–1948)

Outcome	Not referred		Referred
	No previous affected infant*	Previous affected infant	
No clinical disease	15	7	0
Recovered	23	7	14
Died, no kernicterus	4	2	4
Kernicterus	9	1	5
Stillborn	5	7	20
Totals	56	24	43

* Includes 11 mothers sensitized by transfusion.

erythroblastosis fetalis in the family, and in the group where a previous affected infant has occurred. The difference might be interpreted as representing a specific effect of exchange transfusion in treatment during the latter period, but the observed differences are not statistically significant ($\chi^2 = 2.11$, $p = 0.1$).

On the other hand, data will be presented in detail in a subsequent communication[12] which show that there is a large positive correlation between the likelihood of a bad result in a live born infant, particularly of kernicterus, and a shortening of the period of gestation to less than 38 weeks, particularly when the titer of maternal antibody is high (1 : 64 or more). Table 5 summarizes these data for the Boston Lying-in Hospital and in addition indicates that during the past four years a practice of early induction of labor has increased the number of babies whose gestatory periods are less than 38 weeks. For example, of 15 babies who developed kernicterus during the period 1945-1948, 9 followed labors induced, because of maternal sensitization, before 38 weeks' gestation.

Data from the Children's Hospital, which will be presented later, will show that during

TABLE 5

RELATION OF OUTCOME TO INDUCTION, TITER AND GESTATION
(Boston Lying-in Hospital, 1945–1948, Live Born Only)

		Induced Labor		Not induced	
		Less than 38 wk. gestation	38 wk. and over	Less than 38 wk. gestation	38 wk. and over
Highest prepartum maternal titer less than 1:64*	Recovered	5	7	7	21
	Died, no kernicterus	1	0	1	1
	Kernicterus	1	1	0	0
Highest prepartum maternal titer 1:64 or higher*	Recovered	4	4	3	6
	Died, no kernicterus	1	0	3	0
	Kernicterus	6	1	1	0
Prepartum titer not known	Recovered	2	0	0	7
	Died, no kernicterus	1	0	2	0
	Kernicterus	2	0	2	1

* Highest titer in bovine albumin.

the period 1947-1948, while induction of labor per se showed no significant correlation with the likelihood of a bad result, a gestation of less than 38 weeks showed a highly significant positive correlation. Analysis of these data has virtually eliminated the possibility that the observed effect of shortened gestation is simply the result of the fact that induction of labor was done to deliver a group of infants with inherently bad prognosis.

The authors have long been aware[9] of a possible detrimental effect of early induction of labor on the prospects of babies who might be live born at term, and for the last year of this study (1948) the policy at the Boston Lying-in Hospital with regard to early induction has been a good deal more conservative than before. Table 6 indicates that the change in mortality of erythroblastosis fetalis seen in the years 1947-1948 has taken place entirely in the group of patients born in 1948, although exchange transfusion was used to about the same degree in both years. Of the five cases of kernicterus seen in 1947, all were the issue of labor induced before 38 weeks' gestation, and four received exchange transfusion. The single case of kernicterus in 1948 was delivered by cesarian section at 34 weeks' gestation after the spontaneous onset of labor. No exchange transfusion was done. It

TABLE 6

RELATION OF OUTCOME TO INDUCTION AND EXCHANGE TRANSFUSION
(Boston Lying-in Hospital, 1947–1948)

	1947		1948	
Recovered	15		20	
Died, no kernicterus	2		1	
Kernicterus	5		1	
Induced		11		2
Not induced		11		20
Exchange transfusion	14		12	
No exchange	8		10	
Stillborn		10		7

seems altogether probable, therefore, that the improved mortality in the 1947-1948 period is no effect of exchange transfusion but represents the result of greater conservatism in regard to induction of labor in sensitized women. This change in mortality is not significant when 1948 is compared with 1947, but is of statistical significance if the experience of the three previous years (1945-46-47), which are comparable, is taken as the standard of comparison.

TABLE 7

GESTATION OF STILLBORN ERYTHROBLASTOSIS FETALIS
(Boston Lying-in Hospital, 1937–1948)

Gestation	1937–1940		1941–1944		1945–1948	
	Not referred	Referred cases	Not referred	Referred cases	Not referred	Referred cases
Less than 32 wk.	1	1	1	0	4	11
32–35 wk.	2	3	5	1	4	8
36–37 wk.	1	0	0	0	3	1
38–40 wk.	3	0	7	1	1	0

There is no doubt that during the last four years of this study, certain babies have been born alive with induction of labor before 38 weeks' gestation who would have been stillborn if pregnancy had been allowed to continue to a later date. On the other hand, in certain babies who would have been live born at term, a bad result has likely been dependent upon immaturity related to early induction. A final evaluation of the role of early induction of labor in the management of erythroblastosis fetalis will have to wait upon more satisfactory information than is now available on the relation of likelihood of stillbirth to advancing gestation or upon the development of some means of prevention of kernicterus. In the authors' case material, as indicated in table 7, advances in serologic technic beginning with 1945 led to the recognition of a number of stillbirths at rather early periods in pregnancy as being due to the Rh factor, where formerly they were not recognized as such in the absence of the full-blown picture of hydrops fetalis. At the same time a number of stillbirths at periods later than 37 or 38 weeks' gestation began to be avoided through early induction of labor in many women known to be sensitized. The exact number is not known, but from the available data concerning stillbirth in the not-referred group of cases in the years 1937-1944, it is estimated that about 10 such stillbirths have been averted in the past four year period, half in the not-referred and half in the referred group. This has apparently been accomplished at considerable risk to the live born infant of less than 38 weeks' gestation.

CONCLUSIONS

The authors have presented a 12 years' survey of mortality changes in erythroblastosis fetalis at a children's hospital and in a hospital devoted to obstetric care. It has been shown that observed changes in mortality rates cannot be interpreted simply in terms of the therapeutic value of any procedure used in management of the sensitized mother or her infant. Specifically, it is not possible in this series of cases to detect any trend to generally lower mortality with a change in 1941 from the use of Rh-positive blood to Rh-negative blood in treatment, nor is evidence at hand to indicate that exchange transfusion has brought a general improvement in the prognosis of this disease during the two years

(1947-1948) in which it has been available. There is reason, on the other hand, to believe that the use of early induction of labor in the sensitized mother (begun in this clinic late in 1944) may have been responsible for an increased risk to certain live born infants during part of the period covered by this study.

These studies have indicated that hesitancy is necessary in ascribing any observed change in mortality of erythroblastosis fetalis to any therapeutic measure the use of which is associated with a change in the nature of the case material being studied. Such changes in clinical material may not become apparent for months, even when a relatively large number of cases is being treated, and will surely vitiate conclusions regarding the merit of therapeutic procedures unless adequate controls are set up. Such difficulties will undoubtedly complicate the interpretation in most centers of the value of exchange transfusion or the use of the so-called "Rh hapten."[13]

It seems certain that the body of clinical material afforded by a large obstetric service is superior to that entering a children's service so far as concerns the reliability of therapeutic and other inferences which may be drawn from study. When the effect of referred cases is taken into account, such case material consists of a fairly representative section of the community so far as Rh problems are concerned. The authors have taken advantage of this fact in making a comprehensive survey of the cases of erythroblastosis fetalis seen at the Boston Lying-in Hospital since 1945, which has indicated that a number of elements have a bearing on outcome or prognosis in individual cases. These studies, which will be reported in detail in subsequent communications,[12, 14, 15] indicate that there are certain factors operating in individual cases which often far outweigh in importance any therapeutic consideration so far as indicating the probable outcome of erythroblastosis fetalis. It is clear that any evaluation of methods of therapy which does not carefully integrate these individual factors may arrive at erroneous conclusions. In the present study, for instance, the question of gestatory age of the infant has been found of paramount importance in the interpretation of a change in mortality rate seen since the use of exchange transfusion was begun.

It is decidedly not intended in presenting these data to disparage the use of exchange transfusion in the treatment of erythroblastosis fetalis. Details of experience with more than 200 exchange transfusions will be reported elsewhere.[16]

Summary

1. Twelve years' experience with 539 cases of erythroblastosis fetalis has been reviewed.

2. It is not possible to show beyond the statistical limits of chance that any change in mortality of erythroblastosis fetalis in relation to therapy in live born infants has occurred in this time.

3. It is probable that the early induction of labor has caused an increased risk to live born babies during part of this period, when erythroblastosis fetalis has been complicated by immaturity, particularly before 38 weeks' gestation.

4. Caution is urged in assaying the value of any therapeutic measure, the use of which in erythroblastosis fetalis may result in a selected body of clinical material.

Note: This paper was prepared in April 1949, and presented in part at the meeting of the Society for Pediatric Research in May 1949. The discovery that exchange transfusion of blood from female donors has a strikingly and uniquely beneficial effect on babies with erythroblastosis fetalis[16] is of more recent date (July 1949). The conclusions drawn in this paper are still valid.

ACKNOWLEDGMENT

The authors are indebted to Miss Margaret Drolette for assistance in the compilation of the statistical material.

REFERENCES

1. Levine, P., Katzin, E. M., and Burnham, L., Isoimmunization in pregnancy: Its possible bearing on etiology of erythroblastosis fetalis, J.A.M.A. **116**:825, 1941.
2. Levine, P., Burnham, L., Katzin, E. M., and Vogel, P., Role of iso-immunisation in pathogenesis of erythroblastosis fetalis, Am. J. Obst. & Gynec. **42**:925, 1941.
3. Diamond, L. K., Clinical importance of Rh blood type, New England J. Med. **232**:447 and 475, 1945.
4. Wallerstein, H., Substitution transfusion: New treatment for severe erythroblastosis fetalis, Am. J. Dis. Child. **73**:19, 1947.
5. Wiener, A. S., and Wexler, I. B., Results of therapy of erythroblastosis with exchange transfusion, Blood **4**:1, 1949.
6. Diamond, L. K., and Abelson, N. M., Demonstration of anti-Rh agglutinins: Accurate and rapid slide test, J. Lab. & Clin. Med. **30**:204, 1945.
7. Diamond, L. K., and Denton, R. L., Rh agglutination in various media with particular reference to value of albumin, J. Lab. & Clin. Med. **30**:821, 1945.
8. Danis, P. G., Eto, J. K., and Sennott, J. S., Use of Rh-positive blood cells in treatment of erythroblastosis fetalis, J. Pediat. **28**:457, 1946.
9. Vaughan, V. C., III, Kernicterus in erythroblastosis fetalis, J. Pediat. **29**:462, 1946.
10. Parsons, L., Clinician and Rh factor, Lancet **1**:815, 1947.
11. Darrow, Ruth R., and Chapin, Josephine, Pathogenesis of passive Rh isoimmunization in newborn (erythroblastosis fetalis), Am. J. Dis. Child. **73**:257, 1947.
12. Allen, F. H., Jr., Diamond, L. K., and Vaughan, V. C., III, Erythroblastosis fetalis. II. Prognosis in relation to history, maternal titer and length of fetal gestation, PEDIATRICS, to be published.
13. Carter, Bettina B., Rh hapten: Its preparation, assay, and nature, J. Immunol. **61**:79, 1949.
14. Diamond, L. K., Vaughan, V. C., III, and Allen, F. H., Jr., Erythroblastosis fetalis. III. Prognosis in relation to clinical and serologic manifestations at birth, PEDIATRICS, to be published.
15. Vaughan, V. C., III, Allen, F. H., Jr., and Diamond, L. K., Erythroblastosis fetalis. IV. Further observations on kernicterus, PEDIATRICS, to be published.
16. Allen, F. H., Jr., Diamond, L. K., and Watrous, J. B., Jr., Erythroblastosis fetalis. V. Value of blood from female donors for exchange transfusion, New England J. Med. **241**:799, 1949.

SPANISH ABSTRACT

Eritroblastosis fetalis. Dificultades en la interpretacion de diferencias de mortalidad

En un "survey" realizado durante un periodo de experiencia de doce años en el Boston Lying-in Hospital y el Boston Children Hospital fue imposible demonstrar una baja significante de mortalidad entre el grupo de niños con eritroblastosis fetalis tratados solamente con transfusiones de sangre de tipo Rh negativo; el grupo de niños en el cual las madres fueron inducidas tempranamente en el parto y el grupo de niños tratados con "transfusiones de exsanguinacion."* Sin embargo se observó que en el grupo de niños producto de una induccion temprana del parto, ocurrió un aumento significante de la mortalidad, particularmente en aquellos casos en los cuales el periodo de gestacion fue menos de 38 semanas.

Sé pudo demostrar que las diferencias favorables de mortalidad en cierto grupo de casos observado durante ese periodo, en parte dependio de lo diverso del material clinico estudiado. En la interpretación de resultados aparentemente favorables debe tenerse en cuenta las diferencias clinicas peculiares de la afeccion. Los autores sugieren que los resultados de este estudio no deben interpretarse como condenativo de la "transfusion de exsanguinacion" la cual continua siendo una forma segura y efectiva en el tratamiento de la eritroblastosis fetalis.

* La "transfusion de exsanguinacion" (Exchange Transfusion) se refiere a la substitucion total de la sangre del paciente poe sangre de tipo Rh negativo.

300 Longwood Avenue

USE OF PARENTERAL POTASSIUM THERAPY IN SURGICAL PATIENTS

Its Role in Preventing Chloride Loss

By CHARLES UPTON LOWE,* M.D., MARGARET ROURKE, ELSIE MACLACHLAN, B.S., AND ALLAN M. BUTLER, M.D.
Boston

IT HAS been observed frequently that following surgery patients may have a low serum chloride concentration.[1-2] The shocklike state which occasionally occurs has been assumed to be the result of this low serum Cl.[3] Therapy as radical as parenteral use of dilute hydrochloride acid has been advocated.[4-6] Animal experiments[7-11] indicate that when there is a deficit of potassium and an excess of sodium within the cells, the concentration of Cl in the plasma decreases while that of HCO_3 increases. With the ingestion of K there is a retention of Cl and rise in serum Cl. Such changes in tissue and serum concentration also occur in the hyperadrenalism of Cushing's syndrome[12-14] and of the alarm reaction in rats.[15] That such an alarm reaction may result from operations is indicated by a fall in circulating eosinophiles and an increase in urinary 11-oxycorticoids.[16] Moreover, such starvation and parenteral saline as may be incident to operation favor these alterations in tissue and serum concentrations.

The following studies were undertaken to determine whether the use of parenteral K in surgical patients would increase the intracellular potassium concentration and prevent a loss of Cl from the body. The results augment the affirmative evidence that has been accumulating since these studies were made.[17-22]

PLAN OF STUDY

Five patients with surgical disease were studied. Those patients that were chosen had no stools during the period of observation. Two infants, 21 mo. and 7 mo. of age, had intussusception. Three children had perforated appendices with peritonitis, two 9 yr. old and one 14. The 2 children (S.L. and A.B.), who were the same age and weight and had perforated appendices, were felt to be ideal subjects for comparison between the 2 types of therapy. Therefore, throughout periods of study one (S.L.) received Na, Cl and glucose, the other (A.B.) a similar regime to which K had been added.

Alimentation was entirely by vein. Periods of collection started as soon as possible after the patient entered the hospital and had voided or had been catheterized. Operation was performed within the 1st 12 hr. All collections were in 12 hr. batches or as nearly so as possible and there were twenty-two 12 hr. periods in all. It was felt justifiable to run periods as short as 12 hr. under the circumstances of these studies since gastrointestinal absorption could play but a negligible part in the balanced achieved. No attempt was made to estimate the losses that occurred during operation due to blood loss and tissue removed. Although these might have been considerable, they were present in each patient and

From the Children's Medical Service of the Massachusetts General Hospital and the Department of Pediatrics, Harvard Medical School, Boston.

Read at the Annual Meeting of the Society for Pediatric Research, Atlantic City, May 4, 1949.
Supported in part by a grant from Swift and Company.
(Received for publication Dec. 1, 1949.)

* National Research Council Fellow.

failure to include such losses in the calculations should not invalidate the comparisons in the losses and balances which follow.

Material removed by gastrointestinal suction and urines were analyzed for Na, Cl, K and N. The methods used were described in a previous communication from this laboratory.[23]

Results

Inspection of the balance data (tables 1-5) permits one to observe the following: 1. Potassium was consistently present in the urine of all patients; hence those patients receiving no potassium ion were always in negative potassium balance. 2. In only 3 of 13 periods during which K was administered was there a negative potassium balance. 3. Although gastric suction caused the loss of considerable H_2O and electrolyte, in most instances it accounted for only a small fraction of the total potassium loss.

Table 6 presents for purposes of comparison the data on the two children, SL. and AB., whose clinical data were so similar but whose therapy differed, the one receiving K, the other none. Each child was studied for five 12 hour periods. Both children received approximately the same water intake. Child AB., who received K, also received slightly more Na and Cl. However, the number of milliosmoles of electrolytes excreted during the

TABLE 1

Balance Data, PD., 7 Mo., 6.4 kg., Male, Intussusception, 12 hr. Periods

Period		Na mEq.	Cl mEq.	K mEq.	Water cc.	Serum mEq/l.
	Intake	19.2	14.7	0.38	505	Na 126§
	(IWL)*				(90)	Cl 93
I	Output DD†	2.15	5.84	0.30	90	CO_2 20.5
	Urine	11.30	11.30	5.36	185	
	Balance	+5.75	−2.44	−5.28	+(140)	
	Intake	3.0‡			440	
	(IWL)				(90)	
II	Output DD	4.08	7.74	0.56	50	
	Urine	0.67	1.05	1.92	85	
	Balance	−1.75	−8.79	−2.48	+(215)	
	Intake	34.5	19.0	8.25	835	
	(IWL)				(90)	
III	Output DD	5.0	10.2	0.92	200	
	Urine	0.70	6.22	2.49	415	
	Balance	+28.8	+2.58	+4.84	+(130)	
	Intake	11.1	7.4	5.5	515	Na 141**
	(IWL)				(90)	Cl 93
IV	Output DD	6.28	8.56	0.65	190	K 3.2
	Urine	1.94	5.60	1.53	170	CO_2 30.8
	Balance	+2.88	−6.76	+3.32	+(64)	
	Cumulative Balance	+35.68	−15	+0.4	+(549)	

* Insensible Water Loss—500 cc./m²/24°.
† Duodenal Drainage.
‡ Na from Sodium Sulfadiazine.
§ Immediately before therapy started.
** At completion of balance studies.
( ) Calculated.

TABLE 2

BALANCE DATA, RP., 21 MO., 9.6 KG., MALE, INTUSSUSCEPTION, 12 HR. PERIODS

Period		Na mEq.	Cl mEq.	K mEq.	Water cc.	Nitrogen gm.	Serum mEq./l.
	Intake	35.3	28.7	6.38	645		Na 132‡
	(IWL)*				(100)		Cl 98
I	Output DD†	11.9	12.25	1.07	175	0.165	K 4.4
	Urine	6.09	4.28	4.55	165	0.836	
	Balance	+17.31	+12.17	+0.76	+(205)	−1.001	
	Intake	19.8	14.5	13.2	750		Na 140
	(IWL)				(100)		Cl 102
II	Output DD	15.47	16.92	2.54	235	0.129	K 5.8
	Urine	14.25	9.24	3.38	385	0.528	
	Balance	−9.92	−11.66	+7.28	+(30)	−0.657	
	Intake	18.5	13.5	12.3	705		
	(IWL)				(100)		
III	Output DD	0	0	0	0		
	Urine	22.10	12.6	8.10	450	0.284	
	Balance	−3.60	+0.9	+4.2	+(155)	−0.284	
	Intake	17.7	13.0	11.8	670		Na 138.9§
	(IWL)				(100)		Cl 106
IV	Output DD	0	0	0	0		K 4.9
	Urine	15.28	11.05	5.2	325	0.237	CO_2 27.9
	Balance	+2.42	+1.95	+6.6	+(245)	−0.237	
	Cumulative Balance	+6.21	+3.36	+18.84	+(635)	−2.178	

* Insensible Water Loss − 500 cc./m²/24°.
† Duodenal Drainage.
‡ Immediately before therapy started.
§ At completion of balance studies.
( ) Calculated.

periods of collection was smaller and the urinary volume was ⅓ less than the urinary volume of SL., who received no K. The total urinary N of both patients was almost equal.

Further comparison between these two patients is possible from the data of table 7. The normal ratio of Na to Cl in the extracellular fluid is 1.3:1. The ratio of Na to Cl in the fluid administered to SL. was 1:1, and to AB. 1.1:1. There was a marked difference between these two children. Child AB., receiving K, retained more than four times as much Cl as the child who did not.

Unfortunately, the difficulties in weighing these patients prevented obtaining accurate weights for each 12 hour balance period. To obtain information pertaining to extra- and intracellular fluid and electrolyte changes, water balance was estimated by assuming a figure for insensible water loss of 500 cc./m² body surface/day. Water balances* so obtained, and calculations predicated upon the fact that Cl remains extracellular,[24] suggest that AB., who received potassium therapy (table 7) hydrated his extracellular compartment quite adequately while SL. did so only moderately well. Approximately equal amounts of intracellular H_2O were retained by both children. AB. also retained Na pre-

* Water of oxidation was not included in water "intake."

dominately in his extracellular fluid while SL., who did not receive K, retained Na predominately in his intracellular fluid. AB. had a definite positive corrected potassium balance and SL. a negative one. These potassium balances represent the excess K above that accounted for by tissue catabolism as determined by nitrogen balances.

The balance data on the other three patients do not permit such an appraisal of the effect of K on extra- and intracellular H_2O and electrolyte balances. However, plotting

TABLE 3

BALANCE DATA, HE., 14 YR., 52 KG., MALE, PERFORATED APPENDIX WITH PERITONITIS, 12 HR. PERIODS

Period		Na mEq.	Cl mEq.	K mEq.	Water cc.	Serum mEq./l.
	Intake	0	0	0	1000	
	(IWL)*				(390)	
I	Output DD†	0	0	0	0	
	Urine	2.9	12	12.5	. 250	
	Balance	−2.9	−12	−12.5	+(360)	
	Intake	77	68	21	1650	Na 129
	(IWL)				(390)	Cl 97
II	Output DD	82	78	4.2	975	K 4.6
	Urine	3.26	15	9	375	
	Balance	−8.26	−25	+7.8	−(90)	
	Intake	141	131	24	1900	
	(IWL)				(390)	
III	Output DD	4.1	3.85	0.024	80	
	Urine	14	47.5	21.3	720	
	Balance	+123	+79.75	+2.7	+(710)	
	Intake	125	122	8	1075	Na 133
	(IWL)				(390)	Cl 96
IV	Output DD	44	37	0.171	330	K 5.1
	Urine	17.7	29	19	465	
	Balance	+63	+56	−11.17	−(110)	
	Cumulative Balance	+175	+99	−13.17	+(872)	

* Insensible Water Loss—500 cc./m²/24°.
† Duodenal Drainage.
( ) Calculated.

the chloride balances against the ratio of Na to Cl urinary excretion appears to support the importance of K in chloride conservation. In chart 1 the ordinate plotted on a logarithmic scale represents the ratio between Na and Cl in the urine and the abscissa the chloride balance. The two dark intersecting lines are drawn through the abscissa at "O" chloride balance, and through the ordinate at the point where the ratio between the sodium concentration and the chloride concentration in the urine was equal to 1. In other words, when a patient excreted more Cl than Na in his urine that period is represented by a point below the horizontal line; if he excreted more Na than Cl, the point is above the horizontal line. If the chloride balance is positive, the period is plotted to the right of the vertical line, and if the chloride balance is negative, it is to the left. The dark circles represent those periods during which a patient received no potassium

TABLE 4

BALANCE DATA, SL., 9 YR., 27 KG., FEMALE, PERFORATED APPENDIX, 12 HR. PERIODS

Period		Na mEq.	Cl mEq.	K mEq.	Water cc.	Nitrogen gm.	Serum mEq./l.
	Intake	60	60	0	1335		Na 138.8**
	(IWL)*				(200)		Cl 95
I	Output DD†	6.0‡	14‡	1.6‡	200		K 4.2
	Urine	5.95	14.5	18.7	725	6.61	
	Balance	+48	+31.5	−20.3	+(210)	−6.61	
	Intake	22.5	22.5	0	920		Na 134.7
	(IWL)				(200)		Cl 100
II	Output DD	17.8	35.2	4.31	525	0.304	K 3.7
	Urine	5.43	15.8	4.22	310	2.7	CO_2 25.7
	Balance	−0.73	−28.5	−8.53	−(115)	−3.064	
	Intake	67.5	67.5	0	1035		
	(IWL)				(200)		
III	Output DD	11.1	30	3.45	410	0.180	
	Urine	36.3	43.7	7.61	1120	3.14	
	Balance	+20	−6.2	−11.06	−(705)	−3.320	
	Intake	68	68	0	1205		Na 139.9
	(IWL)				(200)		Cl 103
IV	Output DD	4.59	10.8	0.97	140	0.062	K 3.9
	Urine	49.5	49.7	5.88	700	1.88	CO_2 28.4
	Balance	+14	+7.5	−6.85	+(165)	−1.942	
	Intake	48	48	0	1355		Na 135.6§
	(IWL)				(200)		Cl 98
V	Output DD	0	0	0			
	Urine	12.6	15.3	2.25	225	0.848	
	Balance	+35.4	+32.7	−2.25	+(930)	−.848	
	Cumulative Balance	+117	+37	−48.99	+(485)	−15.74	

* Insensible Water Loss—500 cc./m²/24°.
† Duodenal Drainage.
‡ Estimated.
§ At completion of balance studies.
** Immediately before therapy started.
( ) Calculated.

therapy, while the light circles represent those periods during which potassium therapy was administered. Each circle represents one 12 hour collection. During only one period when a patient received no potassium therapy did he excrete more Na than Cl in his urine. This single collection was obtained during Period 1 of patient AB. while he was receiving only glucose and H_2O by vein. Five of the nine periods without potassium therapy lie to the left of the midline and below the horizontal line indicating that during these five periods the patients were in negative chloride balance and unable to conserve Cl in the process of urinary excretion. In marked contrast, all but one patient receiving potassium therapy provided a defense against a negative chloride balance, by conserving Cl in the process of renal excretion.

The five dark circles in chart 1 in the lower left hand corner (negative chloride balance and Cl greater than Na in the urine) represent periods during which the material obtained by gastric suction contained more Cl than Na. Furthermore, in 17 of the 22 periods the ratio of Na to Cl in the parenterally administered fluid was similar to that pertaining in extracellular fluid, and in no instance was more Cl than Na administered. It therefore seems unlikely that the NaCl composition of either the fluid administered or removed by gastric suction could have been responsible for the excessive urinary loss of Cl in the presence of a negative chloride balance.

TABLE 5

BALANCE DATA, AB., 9 YR., 27 KG., MALE, PERFORATED APPENDIX AND PERITONITIS, 12 HR. PERIODS

Period		Na mEq.	Cl mEq.	K mEq.	Water cc.	Nitrogen gm.	Serum mEq./l.
	Intake	0	0	0	1200		Na 130‡
	(IWL)*				(200)		K 4
I	Output DD†	4.14	14.8	1.26	140	0.357	Cl 100
	Urine	1.95	0.37	7.18	104	1.842	
	Balance	−6.09	−15.17	−8.44	+(756)	−2.199	
	Intake	34	26	20	1070		
	(IWL)				(200)		
II	Output DD	9.40	33.6	3.75	395	0.438	
	Urine	13.1	9.7	26.8	570	4.88	
	Balance	+11.5	−17.3	−10.55	−(95)	−5.318	
	Intake	105	100	13.5	1240		Na 130
	(IWL)				(200)		K 4.3
III	Output DD	4.3	19.3	2.57	265	0.154	Cl 100
	Urine	4.1	0.53	14.3	295	2.755	CO_2 29.5
	Balance	+96.0	+80.17	−3.37	+(480)	−2.909	
	Intake	70	63	18	1180		
	(IWL)				(200)		
IV	Output DD	6.0	26.2	2.88	335	0.164	
	Urine	18.2	2.12	14.2	415	3.485	
	Balance	+45.8	+34.7	+0.92	+(230)	−3.649	
	Intake	106	94	17.5	1380		Na 136
	(IWL)				(200)		K 4.4
V	Output DD	0.58	2.1	0.33	30	0.165	Cl 104
	Urine	32.7	7.1	7.8	640	2.280	CO_2 28.4
	Balance	+72.7	+84.8	+9.37	+(510)	−2.445	
	Cumulative Balance	+220	+167	−12.07	+(1881)	−16.520	Na 134§
							K 3.9
							Cl 101

* Insensible water loss—500 cc./m²/24°.
† Duodenal drainage.
‡ Immediately before therapy started.
§ At completion of balance studies.
( ) Calculated.

TABLE 6

COMPARISON OF INTAKE AND URINARY OUTPUT, PATIENTS SL. AND AB. OVER FIVE 12 HR. PERIODS

Intake	SL. Receiving No Potassium	AB. Receiving Potassium
H_2O cc.	5850	6070
Na mEq.	266	315
Cl mEq.	266	283
K mEq.	0	69
Urine		
Volume cc.	3080	2024
Milliosmoles	296	280

DISCUSSION AND CONCLUSION

These balance studies supplement the observations of others[9, 10, 17-19, 22] that, in patients suffering fasting, dehydration and intracellular potassium depletion due to an alarm reaction or to an alkalosis resulting from loss of gastric Cl, parenteral administration of isotonic NaCl may be ineffective in accomplishing extracellular repair due to Na going with H_2O to the dehydrated and potassium depleted cells, and Cl being excreted in the urine. When such therapy is modified by decreasing the ratio of Na to H_2O and adding K, there is a more physiologic hydration of both fluid compartments of the body, Cl being conserved by the kidneys and Na tending to stay in its proper extracellular position. Similar conservation of urinary Cl and elevation in serum Cl has been noted following

TABLE 7

COMPARISON OF SELECTED METABOLIC DATA, PATIENTS SL. AND AB. OVER FIVE 12 HR. PERIODS

	Pt. SL. Receiving No Potassium	Pt. AB. Receiving Potassium
Ratio $\frac{Na}{Cl}$ Administered	$\frac{1}{1}$	$\frac{1.1}{1}$
Ratio $\frac{Na}{Cl}$ H_2O_E (normal)	$\frac{1.3}{1}$	$\frac{1.3}{1}$
Ratio $\frac{Na}{Cl}$ Retained	$\frac{3.16}{1}$	$\frac{1.3}{1}$
Cl mEq. balance	+37	+167
K mEq. balance (corrected)*	−9	+29
H_2O_E† cc. balance	+160	+1416
H_2O_I† cc. balance	+775	+889
Na_E† mEq. balance	0	+220
Na_I† mEq. balance	+117	0

* Corrected for protein catabolism assuming 2.7 mEq. K/gm. N in tissue and thus representing the K from or to intact cells.

† E = extracellular; I = intracellular.

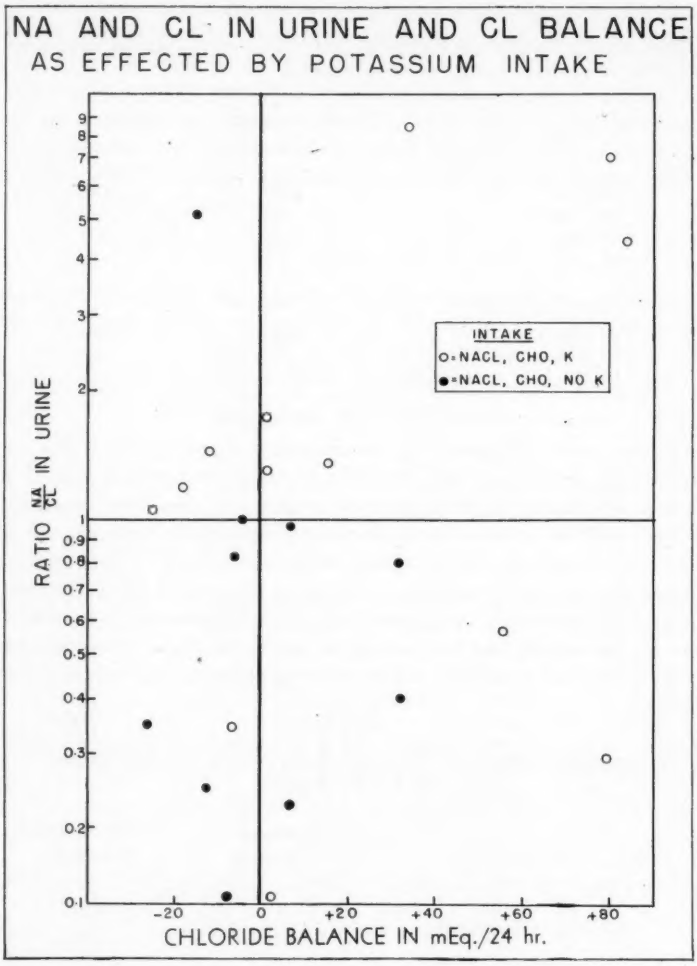

CHART 1

potassium therapy in patients with low serum chloride concentrations associated with ulcerative colitis, where excessive loss of K and Cl in the urine suggests a similar alarm reaction.[25]

REFERENCES

1. Ireneus, C., Jr., Hypochloremic state in surgical patients, Surgery **18**:582, 1945.
2. Abbott, W. E., Chemical alterations occurring in surgical patient and their interpretations, Surgery **20**:770, 1946.
3. Porges, O., Ueber Coma Hypochloraemicum, Klin. Wchnschr. **11**:186, 1932.
4. Hartman, A. F., Acidosis, alkalosis and ketosis, in Brennemann's Practice of Pediatrics, edited by I. McQuarrie, Hagerstown, Md., William F. Prior Company, chap. 24, pp. 14-16.
5. Hartman, A. F., Acidosis and alkalosis, PEDIATRICS **2**:584, 1948.
6. Akin, J. T., Jr., and Forbes, G. B., Congenital hypertrophic pyloric stenosis, Surgery **21**:512, 1947.

7. Heppel, L. A., Electrolytes of muscle and liver in potassium depleted rats, Am. J. Physiol. **127**: 385, 1939.
8. Orent-Keiles, E., and McCollum, E. V., Potassium in animal nutrition, J. Biol. Chem. **140**:337, 1941.
9. Darrow, D. C., Schwartz, R., Iannucci, J. F., and Coville, F., Relation of serum bicarbonate concentration to muscle composition, J. Clin. Investigation **27**:198, 1948.
10. Darrow, D. C., Changes in muscle composition in alkalosis, J. Clin. Investigation **25**:324, 1946.
11. Gardner, L. I., and others, Chloride diarrhea and systemic alkalosis in potassium deficiency, Fed. Proc. **8**:453, 1949.
12. McQuarrie, I., Johnson, R. M., and Zeigler, M. R., Plasma electrolyte disturbance in patient with hypercorticoadrenal syndrome contrasted with that found in Addison's disease, Endocrinol. **21**:762, 1937.
13. Wilson, D. M., Power, M. H., and Kepler, E. J., Alkalosis and low plasma potassium in case of Cushing's syndrome: Metabolic study, J. Clin. Investigation **19**:701, 1940.
14. Kepler, E. J., and others, Adrenal cortical tumor associated with Cushing's syndrome: Report of case with metabolic studies and remarks on pathogenesis of Cushing's syndrome, J. Clin. Endocrinol. **8**:499, 1948.
15. Selye, H., Blood sugar and chloride changes during alarm reaction, Proc. Am. Physiol. Soc., Baltimore, Md., March 1948, p. 181.
16. Uribe, R. C., and others, Observations on adrenal cortical "sugar-fat-nitrogen" hormone production as measured by urinary 11-17-oxysteroid-like substances (11-17-OCS) and by counts of circulating eosinophiles, read before the American Pediatric Society, Atlantic City, May 5, 1949.
17. Blixenkrone-Muller, N., Potassium metabolism in connection with operations, Acta chir. Scandinav. **97**:302, 1949.
18. Pearson, O. H., and Eliel, L. P., Postoperative alkalosis and potassium deficiency, J. Clin. Investigation **28**:803, 1949.
19. Nelson, R. M., Refractory alkalosis and potassium ion in surgery, Surgery, to be published.
20. Tarail, R., and Elkinton, J. R., Potassium deficiency and role of kidney in its production, J. Clin. Investigation **28**:99, 1949.
21. Ballet, S., Nadler, C. S., Gazes, P. C., and Lanning, M., Effect of vomiting due to intestinal obstruction on serum potassium, Am. J. Med. **6**:712, 1949.
22. Mudge, G. H., and Vislocky, K., Electrolyte changes in human striated muscle in acidosis and alkalosis, J. Clin. Investigation **28**:482, 1949.
23. Talbot, N. B., and others, Progeria: Clinical, metabolic and pathologic studies on patient, Am. J. Dis. Child. **69**:267, 1945.
24. Darrow, D. C., Congenital alkalosis with diarrhea, J. Pediat. **26**:519, 1945.
25. McArthur, J. W., and MacLachlan, E., unpublished data.

SPANISH ABSTRACT

El uso parenteral del potasio en pacientes quirurgicos y su función en la prevencion de la perdida de cloruro

Estudios analiticos realizados por los autores corroboran observaciones previas en pacientes sufriendo de inanicion, deshidratacion y perdida celular de potasio debida a "reacciones de alarma" o producida por una alkalosis resultante de la perdidad de cloruro gastrico. La administracion de cloruro de sodio isotonico en estos casos a veces es inefectiva en producir la reparacion celular necesaria debido a que el sodio migra con el agua hacia las celulas deshidratadas y depletas de potasio y el cloruro es eliminado en la orina. Una hidratacion mas fisiologica de ambos compartimientos (intra y extracelular) del cuerpo, puede obtenerse mediante la modificacion de la solucion disminuyendo el "ratio" de sodio y agua y añadiendole potasio. De esta forma el cloruro es conservado por los riñones y el sodio tiende a permanecer en su propia posicion extracelular. Esta conservacion del cloruro urinario y su elevacion en el suero sanguineo fué observada siguiente a la administracion de potasio a pacientes con colitis ulcerativa con concentraciones bajas del cloruro de sodio en el suero. En estos casos de colitis ulcerativas la perdida excesiva de potasio y cloruro en la orina es sugestiva de una "reaccion de alarma" semejante.

University of Minnesota Hospitals

ADRENOCORTICAL FUNCTION IN THE NEWBORN INFANT AS MEASURED BY ADRENOCORTICOTROPIC HORMONE-EOSINOPHIL RESPONSE

By ROBERT KLEIN, M.D., AND JAMES HANSON, M.D.
Baltimore

THIS paper presents an attempt to study adrenocortical function of the newborn infant by measuring the change in circulating eosinophils following the administration of adrenocorticotropic hormone (ACTH) and by making eosinophil counts in the course of various diseases. Knowledge concerning adrenal activity in the neonatal period is especially desirable because of the peculiarities of the fetal adrenal and its development during postnatal life, and because of suggestive evidence of transient hypofunction of the adrenal cortex in early infancy.[1,2] Smith[3] reported electrolyte changes in the neonatal period similar to those seen in animals after administration of desoxycorticosterone has been stopped, and he suggested they may be associated with the degeneration of the fetal cortex which occurs shortly after birth.

METHODS

The majority of the eosinophil counts, and all the early ones, were done on oxalated venous blood by the Dunger method as described by Forsham.[4] The later counts were done by the method of Randolph[5] which is simpler because capillary blood can be used and the counts need not be made immediately.

Several different lots of ACTH* were used. These varied in potency and in the amount of contaminating hormones or other materials; but whenever a child received more than 1 injection of hormone, these were always from the same lot and vial. The ACTH was dissolved in saline and injected intramuscularly immediately after the first blood sample was drawn. A decrease in the number of circulating eosinophils of 37% or more 4 hr. after ACTH administration is called a positive response to ACTH in this paper. Thirty-seven per cent was chosen instead of the 50% fall chosen by Forsham[4] because it was found that in normal children of an older age group the preparations of ACTH used did not often cause a fall of the eosinophil count greater than this. There is no sharp dividing line between normal and abnormal, of course, and an arbitrary division was made knowingly. In a small number of infants under 3 days of age repeated counts were made at 6, 7 or 8 hr. after the administration of ACTH. No significant fall occurred after 4 hr. in these cases. Small doses of 0.7—2 mg. were first used for fear of side reactions from pitressin-like contaminating substances. However, up to 12 mg. of purer material were later used without clinical side reactions. Even the small original dose did cause some rise in blood pressure. No blanching, cramps or distress was ever observed though it is quite possible that these reactions escaped notice in a small proportion of patients.

To demonstrate responsiveness of the eosinophil level of the newborn infant to adrenocortical hormone similar tests were carried out substituting Upjohn's lipoadrenal extract for ACTH.

The patients were babies born on the obstetric service of the Johns Hopkins Hospital. No conscious effort was made at selection, but unfortunately Negro babies are kept in the hospital an average of

From the Department of Pediatrics, Johns Hopkins University School of Medicine, and the Harriet Lane Home of the Johns Hopkins Hospital, Baltimore.

Supported by a grant from the Commonwealth Fund for the study of endocrine problems in childhood, supplemented by the John Howland Memorial Fund.

(Received for publication Oct. 15, 1949.)

* ACTH was supplied by Dr. John R. Mote, Armour Laboratories, Chicago.

only 3 days so that there are disproportionately few Negro children among those tested repeatedly or at an older age. The authors do not believe that this alters the significance of the work. In addition, measurements were made on a few infants in the neonatal period admitted to the infant's ward of the Harriet Lane Home.

Results

As shown in table 1, of 73 children under 7 days of age (all but 6 were under 4 days of age) only 9 had a fall of eosinophils of 37% or more 4 hours after the administration of ACTH.

Of 25 infants tested at seven days or more (on the last hospital day whenever possible), 21 showed a fall in eosinophil levels of 37% or more four hours after the administration of ACTH. Less than this degree of fall is noted as a negative response in the tables.

TABLE 1

Eosinophil Response to ACTH in Reference to Age

Patient's age	Positive response	Negative response	Total
Less than 7 days	9	64	73
7 days or more	21	4	25

Of the total number of 75 newborn infants tested in the first 6 days of life, in addition to the 9 children with what the authors have called positive responses, there were 10 others whose eosinophils fell from 28-35% after ACTH administration. These were listed as negative according to the arbitrary criterion.

When the two groups are analyzed further according to dosages employed, it is apparent from table 2 that there is still a striking difference in response between the two age groups.

TABLE 2

Eosinophil Response to ACTH in Reference to Age and Dose

Dose of ACTH	Positive response	Negative response	Total
	Group I (patients less than 7 days old)		
0.7–1 mg.	3	42	45
2–12 mg.	6	22	28
	Group II (patients 7 days or over)		
0.7–1 mg.	17	4	21
2 mg.	4	0	4

When the lipoadrenal extract was given in doses of 0.5-1.0 cc. to 11 infants in the first two days of life, the following decreases in number of circulating eosinophils were seen four hours after administration: 51%, 47%, 47%, 45%, 44%, 43%, 42%, 38%, 33%, 11%, 9%.

Of the most significance are the results from a group of 14 infants tested within the first four days of life and retested on the 7th to 15th day. Table 3 shows the ages at which the patients were tested, doses used, and results. All but two of the infants who had shown negative responses during the first four days of life showed decreases in cir-

culating eosinophils of 37% or more when retested later. As can be seen, all the infants received in their last tests either the same dose of the same material or one half as much as they received the first time.

Lippman[6] found that the average eosinophil count in 30 infants at one day of life was 370/mm.^{3} and that the count rose to 525 at 30 hours and was 419 at the end of the second day. Our figures are in close agreement. The average eosinophil count for 30 newborn infants on the first day of life was 359 ± 47.* The range was 78-988. The average for 33 infants on the second day was 420 ± 43, with a range of from 75-1100. These figures are much higher than the upper limits of the normal range reported for

TABLE 3

COMPARISON OF ACTH-EOSINOPHIL RESPONSE IN SAME INFANTS AT DIFFERENT AGES

Patient	Initial Measurement			Last Measurement		
	Age hr.	Dose mg.	% Change	Age days	Dose mg.	% Change
1. Di	12	0.7	20% fall	15	0.7	39% fall
2. Br	29	0.7	35% rise	11	0.7	39% fall
3. Ki	29	0.7	5% fall	8½	0.7	37% fall
4. Bu	16	0.7	17% fall	7⅞	0.7	50% fall
5. Os	14	0.7	9% fall	8⅝	0.7	41% fall
6. Di	50	1.0	10% fall	9	1.0	33% fall
7. Ha	33	2.0	47% rise	7½	1.0	48% fall
8. Si	48	1.0	23% fall	9	1.0	43% fall
9. Mi	26	1.0	19% rise	8	1.0	58% fall
10. Me	77	2.0	30% fall	9	1.0	30% fall
11. Ba*	29	2.0	0	9	2.0	50% fall
12. Ni	27	6.0	10% fall	8	2.0	49% fall
13. Ev	17	6.0	8% fall	7¾	2.0	70% fall
14. Fr	26	4.0	42% rise	9	2.0	45% fall

* This patient had a test carried out at exactly 7 days of life which was intermediate in time between the 2 tests noted above. The fall at 7 days was 27%. This is included in the over-all statistics and represents 1 of the 4 negative responses found at 7 days or over.

adults by Hills et al.[7] These workers said that 60-200 was a normal range. It is interesting to note that we have come to accept without question an eosinophil count of less than 450 in older children, and feel that frequently somewhat higher counts are not abnormal in childhood. Uribe[8] has reported similar figures. Lippman further showed that the average eosinophil count fell rapidly at the end of the first week of life. We found that 12 children, 8 to 10 days old, had an average eosinophil count of 268 ± 42, and the range was 63-483. These figures are derived from too small a group of patients to permit a definite statement but they are in the normal range for older children.

Eosinophil counts were made on 12 infants under 2 weeks of age who were admitted to the Harriet Lane Home with the following diagnoses: esophageal atresia, pneumococcus meningitis, erythroblastosis fetalis, congenital heart disease with decompensation, congenital lues, malnutrition, neonatal tetany with convulsions, intestinal obstruction, diarrhea, urinary obstruction and infection. There was no significant difference from the

* The second figure represents the standard deviation.

normal range except in two cases. Although the counts were made as soon as possible after entry into the hospital, it was impossible to say that they were not much lower than the levels of these particular patients before they became ill. Of the two patients with low counts, one was a child who died of pneumococcus meningitis four hours after entry. He was four days old at this time and had a count of 15 eosinophils/mm.^{3} but the total white count was only 2400. The other count below normal limits was found in a 3 day old infant with esophageal atresia. The patient had not been fed, had no pneumonia and was apparently suffering no distress from his anomaly. His count was 10 eosinophils/mm.^{3} It was impossible to grade the severity of disease and its stress in these infants and the authors believe that no significance can be attached to the failure to find more depressed eosinophil levels.

Discussion

Other workers have correlated the eosinophil response with the activity of the "glycogenic corticoids" of the adrenal. The relatively high eosinophil counts and feeble response to ACTH encountered in the early days of life suggest that this activity of the adrenal is diminished after birth but increases between the first and second week of life. Other functions of the adrenal are now being studied. The clinical importance of these observations are obscure. One might speculate that the hypoglycemia regularly found shortly after birth may be related to lack of adrenocortical hormone and that the electrolyte changes observed by Smith[3] might be due to the loss of the relative excess of maternal corticoids and the presence of a period of relative lack of the infants' own cortical hormones. This presupposes that adrenal steroids but not ACTH cross the placental barrier in a manner analogous to that of gonadotropins and estrogen. This situation would inhibit the infant pituitary and the adrenal would be less active as in some cases of Simmonds' disease. We have obtained no evidence that the infant with a disease suffers from lack of adrenocortical hormone. It is not justifiable to assume that poor resistance in the neonatal period is due to lack of sufficient adrenocortical hormone.

Conclusions

ACTH was given to newborn infants and the changes in circulating eosinophils were measured. There was much less response in infants in the first week of life than there was in infants over 1 week of age. Nine out of 11 infants given lipoadrenal extract in the first 2 days of life showed adequate eosinophil falls.

Acknowledgment

The authors gratefully acknowledge the advice and help of Dr. Lawson Wilkins.

References

1. Jaudon, J. C., Hypofunction of adrenals in early life, J. Pediat. **29**:696, 1946.
2. Jaudon, J. C., Hypofunction of adrenals in early life; Further report, J. Pediat. **32**:641, 1948.
3. Smith, C. A., and others, Adjustment of electrolytes and water following premature birth with special reference to edema, Pediatrics **3**:34, 1949.
4. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G., Clinical studies with pituitary adrenocorticotropin, J. Clin. Endocrinol. **8**:15, 1948.
5. Randolph, T. G., Differentiation of leukocytes in counting chamber by propylene glycol-aqueous stain; Screen for detection of major blood abnormalities, Am. J. Path. **8**:48, 1944.
6. Lippman, H. S., Morphologic and quantitative study of blood corpuscles in newborn period, Am. J. Dis. Child. **27**:473, 1924.

7. Hills, A. G., Forsham, P. H., and Finch, C. A., Changes in circulating leukocytes induced by administration of pituitary adrenocorticotrophic hormone (ACTH) in man, Blood 3:755, 1948.
8. Uribe, R. C., and others, Observations on adrenal cortical "sugar-fat-nitrogen" hormone production as measured by urinary 11-17 oxysteroid-like substance (11-17-ocs) and by counts of circulating eosinophils, read at the Annual Meeting of the American Pediatric Society, Atlantic City, N.J., May 1949.

SPANISH ABSTRACT

La Medida de la Funcion Adrenocortical del Recién Nacido Mediante el Uso de la Hormona Adrenocorticotropica (ACTH) y la Repuesta de los Eosinofilos

ACTH fué administrada a recién nacidos y los cambios en el numero de los eosinofilos circulantes fueron estimados. La repuesta de los eosinofilos (eosinopenia) fué mucho menos marcada en los recién nacidos menores de una semana de edad.

De once recién nacidos que recibieron extracto suprarenal lipoidico, en nueve de ellos la repuesta de los eosinofilos (eosinopenia) fue adecuada.

Johns Hopkins Hospital

DOSAGE OF DRUGS IN INFANTS AND CHILDREN: I. ATROPINE

By KLAUS R. UNNA, M.D., KURT GLASER, M.D., EARL LIPTON, M.D., AND PAUL R. PATTERSON, M.D.
Chicago

RECOMMENDED doses of atropine for infants and children of various age groups vary widely. It is generally assumed[1,2] that small children are relatively more resistant to atropine and other autonomic drugs than adults. On the other hand, atropine intoxication in children is of more frequent occurrence than in adults, and it is said[3] that young children are especially susceptible to atropine poisoning. Obviously, such statements, contradicting as they may appear, imply that the tolerance to atropine of the growing child changes with age.

Although the reactions of children to challenging doses of atropine (and other autonomic drugs) have, in the past, frequently been evaluated as an aid in the diagnosis of vagotonia, search of the literature reveals a dearth of controlled studies on the effectiveness of atropine in relation to age. Investigations carried out in the past relied on marked reddening of the skin, pupillary dilatation and acceleration of the heart rate as criteria of effectiveness. These criteria appear to be poorly chosen for a determination of the sensitivity to atropine. Flushing of the skin is a sign of overdosage which occurs usually only after salivation has been markedly depressed. Pupillary dilatation on systemic administration of atropine is observed only with doses which exceed those depressing glandular secretions. Furthermore, such "effective" doses of atropine have not been established by systematic trials of graded doses in individual children. The majority of these studies are based on observations of the effects of no more than one or two widely differing doses. Friedberg,[4] for instance, reports the following effective doses of atropine on hypodermic injections: Ages 0 to 3 years—0.2 to 0.3 mg.; 4 to 7 years—0.3 to 0.4 mg.; 8 to 14 years—0.5 mg. He denies that there is a close correlation between effective dose and body weight. According to his protocols, his conclusions are based on a total of 24 injections of 0.1 to 1.0 mg. in 12 healthy children varying in age from 3 months to 13 years. Ritte,[5] on the other hand, maintains that atropine should always be given in relation to body weight. He found that 9 out of 18 infants or small children (age and weight not stated) reacted with flushing and dilatation of the pupil to a hypodermic injection of 0.025 mg./kg. body weight. One infant of 3 months died following the subcutaneous injection of 0.05 mg./kg. On oral administration, a dose of 0.05 mg./kg. was found "effective" in 37 out of 48 infants tested. Obviously, these doses of atropine cannot claim to be accurate. Due to the criteria employed, they necessarily represent values bordering on the toxic range, and are hardly suited to evaluate the sensitivity of children to atropine.

Other studies on the dosage of atropine are found in the reports by Lindberg,[6] White[7]

From the Departments of Pediatrics and Pharmacology, University of Illinois College of Medicine, Chicago.

(Received for publication Nov. 12, 1949.)

and Benzing.[8] Their observations made on the treatment of pylorospasm are confined mainly to the age group of the first 3 months.

Data available in the literature thus appear inadequate to support such assumptions as a change in sensitivity to atropine depending on age or the existence of a "physiological vagotonia" of the infant. The paucity of experimental data is apparently responsible for the wide variation in the recommended doses and the often expressed uncertainty about the proper dose of atropine in small children. The need for such information prompted the present investigators to initiate studies on the efficacy of atropine and other autonomic drugs under controlled conditions in normal children of different age groups.

The object of this study was to measure the sensitivity of children of various ages to atropine. Sensitivity is defined as a function of the reciprocal of the dose required to produce a given effect, in this case suppression of salivation. The dose must necessarily be expressed as the quantity of drug relative to the quantity of active protoplasm on which it acts. The authors chose to express the quantity of active protoplasm in terms of total body weight. Diverse measures of active protoplasmic mass can, in fact, be derived from, or expressed as, functions of body weight.[9] The relation between two biologic properties and the constants characterizing this relationship have no meaning except as empirically determined values which best fit the observations. In relating drug dose and active protoplasmic mass, the dimension (weight, weight$^{2/3}$, weight times length, surface area) which permits the best correlation of dose and observed effect is most desirable. However, regardless of the degree of correlation, it cannot be implied that the observed response (drug action, metabolic rate, cardiac output) is a function of the dimension used. It is not implied that there is a strict cause-effect relationship between total body weight and response to atropine. It was found that variations in response to doses expressed in terms of body weight were less than those to doses expressed in terms of surface area ($K \sqrt[3]{w^2}$).[10] Furthermore, for practical reasons, correlation to body weight appeared most appropriate since body weight measurements are easily available to the physician.

Material and Methods

Children selected for the study were patients on the pediatric and orthopedic wards. None of the subjects presented signs or symptoms which would conceivably influence their reactivity to atropine. It was impossible to study a number of subjects sufficiently large to allow averages for each year of age. It was decided rather to group the data into the following age groups: 1 to 12 mo., 12 to 36 mo., 3 to 6 yr. and 6 to 12 yr. This grouping, though arbitrary, was chosen with due consideration of certain physiologic factors in the development of the child. Newborn infants (0 to 1 mo.) were grouped separately from infants of 1 to 12 mo. because of the well known physiologic and metabolic peculiarities of the very young infant. In children over 3 yr. active cooperation is possible and, from 6 yr. on, subjective impressions can be reported by the child.

The selectivity of atropine for various organ systems is well known. Depression of salivation is obtained with small doses which are ineffective in accelerating the heart beat, in dilating the pupil, or in diminishing gastrointestinal motility. In order to measure the sensitivity of subjects to the drug, the authors set out to determine the threshold dose which depresses salivation. For this purpose, 2 methods of stimulating salivation were used: (a) by vigorous chewing on gum and (b) by methacholine, a parasympathomimetic drug with very short duration of action. The procedures employed were as follows:

Chewing Test: The older subjects (4 to 12 yr.) were asked to chew vigorously on half a wad of chewing gum, not to swallow but to collect as much saliva as possible in a medicine glass provided. The saliva was collected for a period of 5 min. and measured in a graduate. The chewing test was performed on groups of children about 2 hr. after a standard, light breakfast. Immediately after

the control test the subjects were given a measured amount of atropine in aqueous solution disguised in 1 oz. of milk (milk alone serving as a placebo) or by hypodermic injection, saline being used for controls. The chewing test was repeated 1 hr. after oral administration or 30 min. after hypodermic injection, respectively, since maximal effects of small doses were obtained at this time. In several instances successive chewing tests were carried out at 1 or 2 hr. intervals over a period of 4 to 8 hr. in an effort to determine the duration of action of atropine. Before and throughout the testing period the subjects were under constant observation and kept in bed or sitting on chairs. They were playing or entertained by games and regarded the test itself as a game. No additional fluids were given and chewing in between tests was not permitted. No meals were served on the ward during the

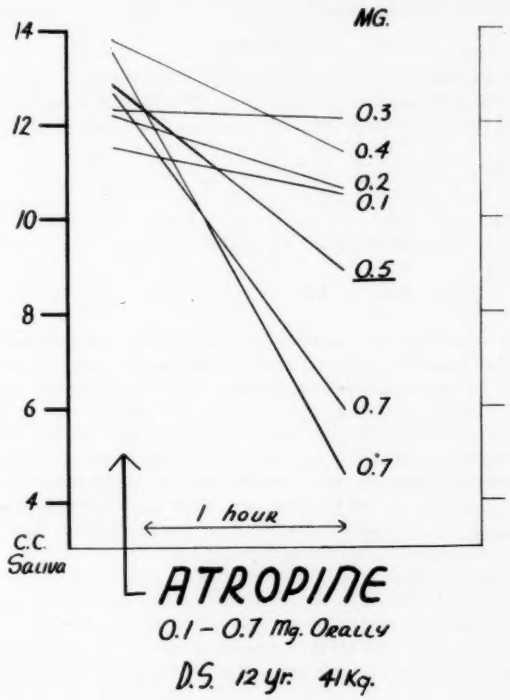

CHART 1. Determination of MED of atropine in child 12 yr. of age by series of "chewing" tests after varying doses of atropine.

tests in order to avoid psychogenic secretion in the subjects. Blood pressure, pulse rate and pupil size were measured before and during the action of atropine. Rectal temperatures were taken occasionally. Children lacking cooperation in the initial tests were excluded from further trials. In those selected for the study, the tests met with excellent cooperation. Optimal results were achieved by competition and rewards.

The volume of saliva obtained within the 5 min. period varied from 4 to 14 cc. in different subjects. The variations did not parallel the age of children, rather they may have reflected differences in hydration although all subjects were assumed to be in normal water equilibrium. However, the amount of saliva elicited by the test was quite constant in the individual child on repeated hourly tests and also from day to day. For instance, on the example presented in chart 1, the amount of saliva during the initial 5 min. chewing period varied from 11.5 to 14.0 cc. on 7 consecutive days.

Numerous tests with placebos administered orally (plain milk) or hypodermically (saline) showed

that the response to repeated chewing tests is almost identical, as evidenced by the example presented in table 1.

The effects of graded doses of atropine were studied repeatedly in each subject. The minimal effective dose (MED) was determined as that amount which—1 hr. after ingestion or 30 min. after hypodermic injection—would diminish the amount of saliva significantly and consistently by approximately 25 to 33%. In each determination of the MED tests were made with subthreshold (ineffective) doses serving as additional controls and with larger than threshold doses which resulted in greater depression of the salivation. The test doses employed for this purpose were varied in 20 to 25% increments. A graphic example of the determination of the MED or threshold dose of atropine is given in chart 1.

Methacholine Test: The blocking effect of atropine on salivation was also tested on stimulation

TABLE 1

CONSTANCY OF SALIVARY RESPONSE IN 9 CHILDREN FOLLOWING PLACEBO MEDICATION. AMOUNT OF SALIVA (CC.) ELICITED OVER 5 MINUTE CHEWING PERIOD

Child No.	1	2	3	4	5	6	7	8	9
Before	9.0	5.9	8.9	6.6	4.8	7.8	5.6	12.6	7.2
	1 hr. after plain milk			1 min. after saline (s.c.)			30 min. after saline (s.c.)		
After	10.1	6.3	11.0	7.3	5.0	7.8	5.0	12.6	6.2

of the salivary glands by methacholine (mecholyl®). Small doses of methacholine were chosen which within 1 to 5 min. after hypodermic injection produce consistently a noticeable increase in salivation. These effects persisted for not more than 10 to 15 min. The methacholine tests were carried out in a manner similar to the chewing tests: a suitable small dose of methacholine for salivary stimulation was first established in repeated tests in each subject. The effects were carefully noted and the amount of saliva measured wherever possible. The minimal dose of methacholine which produced a consistent clinical salivary response was then injected 1 hr. after the oral administration of atropine or ½ hr. after the hypodermic injection. The MED of atropine which significantly depressed the salivary response to the challenging dose of methacholine was determined in repeated tests in the same subject with graded doses of atropine as described for the chewing test.

Comparisons were made of both tests in determination on children of 6 to 12 yr. of age on oral administration of atropine. As evidenced by the results summarized in table 2, the values obtained by both methods are in good agreement. Consequently, stimulation of the salivation by methacholine was used for the determination of the MED of atropine in infants and small children below the age of 4 yr. who cannot cooperate in chewing tests and in whom quantitative collections of saliva are not feasible.

The challenging dose of methacholine was determined individually for each subject. Pupil size and respiratory rate were measured before and at frequent intervals during the effect of methacholine. Particular attention was paid to the signs of increased salivation. In infants, an increase in salivation could be clearly noticed by increased moisture of the lips and drooling. In children of 2 to 4 yr., swallowing movements often appeared to be the best indication for increased saliva flow which was frequently accompanied by rhinorrhea and lacrimation. On individual subjects all observations were made by the same examiner on consecutive days.

Crying immediately following the injection occasionally interfered with the observation. However, with some experience and sufficient repetition of trials it was felt by all observers that the presence (or absence) of increased flow of saliva could be stated with certainty even in infants, although the observations did not allow quantitative estimates comparable to the chewing tests practised by the older subjects.

The individual dose of methacholine selected for the succeeding tests of atropine varied from 0.14 mg. in infants of 1 mo. to 3 mg. in children of 3 yr. The challenging doses chosen produced definite increase in the flow of saliva and often a marked reddening of the skin particularly in the region of the face and neck; sweating of the palms and lacrimation were observed on occasion. They

did not cause signs or complaints of dyspnea, of abdominal cramps or a noticeable fall in blood pressure. On occasion the dose selected accelerated the heart by 6 to 18 beats/min. Children with a history of asthma or diminished vital capacity were excluded from testing with methacholine. The susceptibility to methacholine of children of all age groups will be discussed in a separate publication.

TABLE 2

MED OF ATROPINE IN DEPRESSING SALIVATION IN CHILDREN OF VARIOUS AGE GROUPS

Age Groups	No. of Children	Wt. kg.		Atropine Dose mg.		Atropine—mg./kg. body wt.		Atropine—mg./m.²	
		Range	Average	Range	Average	Range	Average	Range	Average
	Oral Administration								
1 to 12 (1 to 10½) mo.	15	2.9 – 8.5	5.0	.04 –.12*	.077*	.008 –.024	.016	0.155 –0.391	0.268
12 to 36 (12 to 26) mo.	9	6.15–13.8	10.7	.09 –.22*	.15*	.010 –.019	.014	0.130 –0.378	0.273
3 to 6 (4 to 5½) yr.	9	14 –27.3	17.5	.20 –.70†	0.38†	.013 –.041	.022	0.293 –0.935	0.509
6 to 12 yr.	11	17.5 –40	26.3	.3 –.8†	0.48†	.011 –.030	.020	0.150 –0.705	0.453
6 to 12 (7 to 9½) yr.	3	22.2 –36.4	28.9	.4 –.7*	.58*	.018 –.025	.020	0.453 –0.660	0.542
	Hypodermic Administration								
1 to 12 (1 to 8½) mo.	9	3.1 – 8.3	5.8	.009–.04*	.024*	.0024–.0069	.0047	0.0327–0.1240	0.0795
12 to 36 (12 to 26) mo.	5	6.2 –12.5	9.5	.025–.07*	.042*	.0026–.0056	.0043	0.0527–0.1200	0.0863
3 to 6 (4 to 5½) yr.	6	12.7 –18.6	15.1	.06 –.14†	.10†	.0038–.0090	.0066	0.088 –0.174	0.135
6 to 12 (6 to 9½) yr.	4	22.7 –36.4	27.5	.11 –.215†	.156†	.004 –.0075	.0056	0.083 –0.189	0.126

* Salivation produced by methacholine.
† Salivation produced by chewing gum.

In this presentation only those experiments are considered in which the subjects stayed sufficiently long in the hospital to have their threshold dose determined by repeated tests as just described. In more than 100 other children of all ages the number of tests was insufficient to determine the threshold with the desired accuracy. Although their threshold apparently fell in all instances within the range found in the first group, they have been excluded from the evaluation of averages. The data presented here are based on 487 children of both sexes between the ages of 1 mo. and 12 yr.

The efficacy of atropine sulfate freshly prepared in sterile aqueous solution 1:1,000 by the hospital pharmacy was determined following both oral and subcutaneous administration. Attention was paid to possible deterioration of atropine in aqueous solution.[5, 6] However, no indication of diminished potency of the stock solution during periods up to 2 wk. was found. Whenever necessary, a solution of 1:10,000 was prepared by diluting the stock solution with sterile saline.

RESULTS

The results of all experiments are summarized in table 2. The MED are averaged for each of the four age groups and the ranges of the respective doses are given separately.

It is at once apparent that the MED in individual children vary by a factor of 2 or even 3. Individual variations appear to be slightly greater in the younger age groups. Whether this is due only to the greater difficulties in determining the effects of atropine in infants or to a greater variation in the sensitivity to atropine in infants cannot be decided. No subject with abnormal sensitivity or resistance to atropine has been found; none of the subjects deviated from the average of its age group by more than 100%.

The MED caused, only on occasion, effects other than depression of salivation and

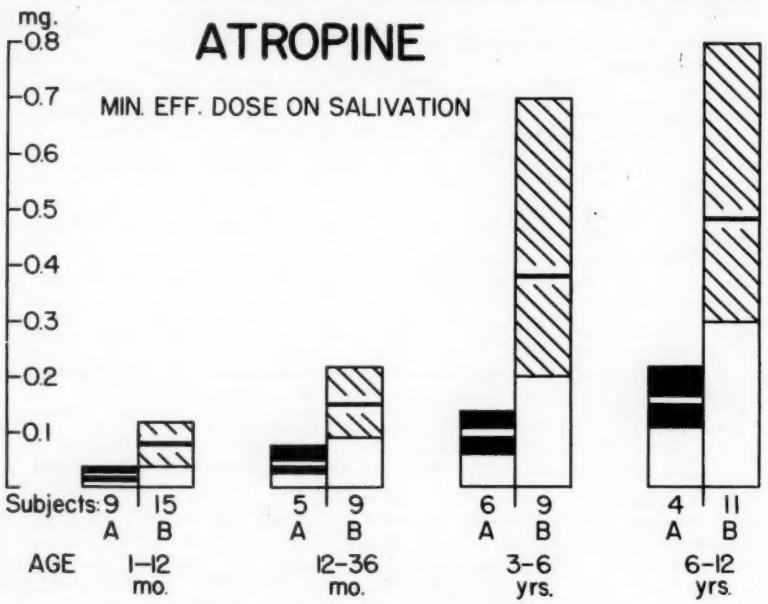

CHART 2. MED of atropine sulfate on salivation in 4 age groups:
A. MED on subcutaneous injection. Average: white line. Range: black parts of columns.
B. MED on oral administration. Average: black line. Range: crosshatched parts of columns.

dryness of the mouth. Significant changes in blood pressure were not observed. The heart rate as a rule was slightly lowered. It is uncertain whether this is an effect of the medication. It may well have been due to the restriction of activity during the rest period. Changes in light intensity during the test made the interpretation of slight differences in pupillary diameter difficult. Significant changes in pupil size were not seen following administration of the MED and change in the light reflex was not noticed. Complaints referable to paralysis of accommodation were not reported by older children.

Flushing of the face and neck was seen in six children between 1 and 18 months of age following the MED. It was mild, occurred about one hour after the oral administration of atropine and persisted for not more than one hour. When the MED was increased by 25% flushing was observed in almost half of all children between the ages of 1 to 3 years, but only on occasion in older children. The erythema never lasted for more than two hours. It was not accompanied by fever. An increase in the MED by one fourth or one third failed to produce an acceleration of the heart rate, and only rarely was there a slight but definite dilatation of the pupil.

The duration of the effect of the MED was measured by chewing tests in older children in a few instances. The depression of the salivation appeared to be greatest between one and two hours after oral administration. It subsided gradually, and no significant diminution in salivary response was obtained four hours after the oral administration of the MED.

A comparison of the MED by hypodermic injection with that by oral administration shows that the oral dose is roughly three times the hypodermic (3.2, 3.6, 3.8 and 3.1 times, respectively, in the four age groups).

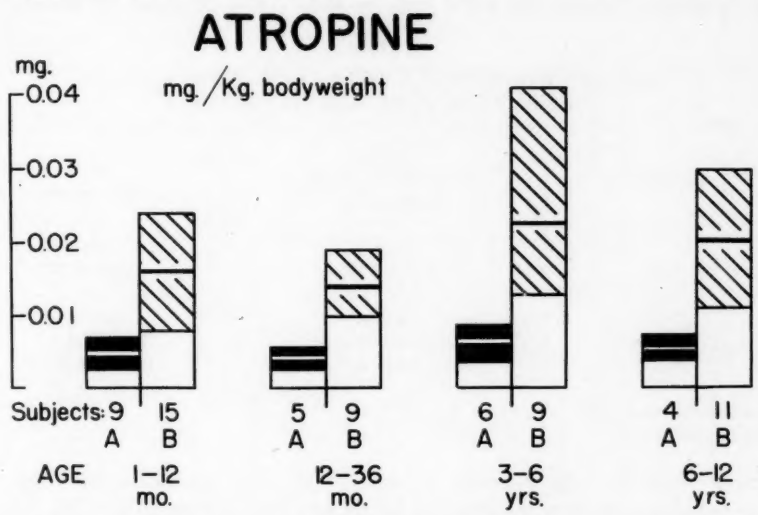

CHART 3. MED of atropine sulfate in relation to body weight in 4 age groups:
A. MED on subcutaneous injection. Average: white line. Range: blackened parts of columns.
B. MED on oral administration. Average: black line. Range: crosshatched parts of columns.

A correlation between the MED and body weight reveals that the variations in the MED within the respective age groups are still remarkably large (compare charts 2 and 3). The range of the MED, absolute or relative to body weight, is about the same in the younger age groups; only in the group from 6 to 12 years a narrower range is observed when the MED is correlated with weight. Thus, children below the age of 6 years seem to have a greater individual variation in sensitivity to atropine than older children.

It was found that the average MED/kg. body weight is about equal in the two age groups from 3 to 6 and from 6 to 12 years, namely, 0.022 and 0.020 mg./kg. on oral administration. The oral doses are 3.3 to 3.5 times as large as the respective hypodermic doses per kg. The MED/kg. is smaller in the younger age groups, from 65% to 83% of the MED/kg. for the older age groups. Since few infants of the newborn period were available for a sufficient time to obtain complete tests, the MED by oral administration was determined in only three newborn babies. The results failed to indicate any significant difference in susceptibility from that of older infants. The values correlated to body weight agreed closely with the average of the MED in infants of 1 to 12 months. It is of interest to note that the MED/kg. is lowest for the age group from 12 to 36 months,

both on oral and subcutaneous administration. The ratio between oral and hypodermic doses in the younger age groups (3.4 and 3.3, respectively) is the same as that obtained in the older groups. The method employed in small children (methacholine test) differed from that used with the older age groups (chewing test). Whether this difference in methods is responsible for the difference in the values obtained cannot be decided. The comparison between the two methods in older children (see table 2) would indicate that, if significant differences exist, they would rather tend to procure a higher MED with methacholine tests.

A correlation between the MED and the surface area calculated by Benedict and

TABLE 3

COMPARISON BETWEEN MED OF ATROPINE ON SALIVATION AND DOSES CAUSING ERYTHEMA, MYDRIASIS AND TACHYCARDIA

Age Group	Test Dose Erythema, Mydriasis, Tachycardia	MED Salivation
0 to 3 yr.	mg. 0.2–0.3 (F)	mg. 0.024–0.042
0 to 10 mo.	mg./kg. oral: 0.05 –0.2 (R) subc: 0.025–0.1 (R)	mg./kg. 0.008–0.024 0.0024–0.0069

F = Data of Friedberg.[4]
R = Data of Ritte.[5]

Talbot's[10] formula is also presented in table 2. The values obtained indicate that there is no better correlation of the MED to surface area than to body weight. The range of the individual MED correlated to weight and to surface has been compared statistically as the ratio of the range to the average (mean). In any given age group, the range expressed as per cent of the mean dose calculated on the basis of surface area was found to equal or exceed the range expressed as per cent of the mean dose calculated on the basis of body weight. Furthermore, the range of all groups expressed as per cent of the mean is greater when doses are expressed in relation to surface area (67%) than when expressed in relation to body weight (43%).

DISCUSSION

A comparison of this data with the effective doses reported by earlier investigators shows that suppression of salivation is a more sensitive criterion for the effects of atropine than flushing or pulse acceleration. The data compiled in table 3 bear evidence that the reactions of general redness of the skin, tachycardia and mydriasis are not suited for a determination of the sensitivity of atropine: Test doses employed by Friedberg[4] are 8 times and those of Ritte[5] about 10 times as large as the MED determined in the present study.

It should be emphasized that the MED reported here are determined on apparently healthy children by their threshold effect on salivation and thus do not represent therapeutically effective doses. The MED may, however, serve as a base line for determining therapeutic doses at the various age levels, and it is of interest to compare them to the doses commonly employed in therapy. In table 4 there are assembled preanesthetic doses

of atropine recommended by Leigh and Belton[11] and Smith[12] together with the MED computed for the same age and body weight. The comparison shows that the doses recommended by Smith[12] exceed the MED by 4:1 in the newborn infant; 3:1 at age 1 to 4 years and 2:1 at age 4 to 12 years. The doses recommended by Leigh and Belton are, at all ages, larger than those of Smith,[12] the greatest difference being found in the newborn infant. Since the MED parallels so closely one half the recommended dose for the age groups from 4 to 12 years, it is surprising to find that this correlation does not hold for infants for whom the recommended doses appear very large indeed.

TABLE 4

COMPARISON BETWEEN MED OF ATROPINE HYPODERMICALLY AND THOSE RECOMMENDED FOR PREANESTHETIC MEDICATION (IN MG.)

Age	Wt. lb.	Leigh and Belton[11]	Smith[12]	MED
0 to 11 mo.	7 to 19	0.15		0.024
Newborn	7		0.065	0.015
11 to 18 mo.	19 to 24	0.15		0.047
1 yr.	21		0.13	0.047
18 to 24 mo.	24 to 27	0.2		0.053
2 to 4 yr.	27 to 35	0.2	0.18	0.06
4 to 6 yr.	35 to 45	0.2–0.3	0.22	0.12
6 to 8 yr.	45 to 55	0.3	0.26	0.13
8 to 10 yr.	55 to 65	0.3	0.32	0.16
10 to 12 yr.	65 to 80	0.6	0.36	0.19

The MED in infants (0.04 to 0.12 mg.) is in excellent agreement with the initial dose generally recommended for the treatment of pylorospasm (1 drop of 1:1000 solution equals 0.05 mg.). When this dose is increased or given too frequently, flushing may be observed, and the desired therapeutic effects are often obtained only when the dose is pushed to the occurrence of mild erythema. This is borne out by the findings that in many infants an increase of 25% in the MED causes flushing. On the other hand, frequent repetition of the medication may lead to increased tolerance as demonstrated by Lindberg,[6] Benzing[8] and others. The present authors' subjects receiving one daily dose over a period of one or two weeks have shown no indication of increased tolerance. A fever reaction to atropine is preceded by flushing, and only notably larger doses will produce fever. When fever followed a single application of atropine,[8] the dose was from two to three times the MED. On the other hand, fever may also result from smaller doses given repeatedly at short intervals,[13] and dehydrated infants are more prone to react with fever than others.

The ratio between oral and hypodermic MED was approximately 3 and consistent in all

age groups. On atropine-resistant children Pilcher[14] found a ratio of 2 to 3, and Ritte[5] using toxic doses of atropine reports a ratio of 2.

The relationship between susceptibility to atropine and age has been studied in dogs, rabbits and rats. Willberg[15] found in 10 week old puppies on intraperitoneal injection of atropine a MLD of 0.23 gm./kg. as contrasted to 0.175 gm./kg. in adult dogs. He assumed that the difference in the development of the central nervous system was responsible for the greater resistance of immature dogs to atropine. However, Schlossmann[16] obtained the opposite results in rabbits on intraperitoneal injection of atropine: The median lethal dose in rabbits below the age of 1 month was 0.225 gm./kg. as compared to 0.35 gm./kg. in older rabbits. In rats the lethal doses (LD_{50}) of atropine following subcutaneous injection[17] showed a remarkable dependence on age, increasing from 0.16 gm./kg. at the age of 10 days to 0.77 gm./kg. in adult rats. This would indicate that the adult rat tolerates almost five times more atropine per body weight than the infant rat. However, Kanda[18] found no significant difference in the lethal doses in rats of various ages when the drug was given by intravenous injection.

All animal studies pertinent to the relation between age and susceptibility to atropine have been carried out with lethal doses, using death as criterion. Furthermore, tolerance to atropine varies enormously from species to species; man is more susceptible to atropine than any animal. The findings failed to show that, on a body weight basis, infants are more resistant to atropine than older children. On the contrary, up to the age of three years their susceptibility to atropine both on oral and hypodermic administration appears to be slightly greater than in the older age groups. Thus, these results do not support the assumption of a physiologic vagotonia, or increased vagal tone, in infants.

The MED established in this study may serve as a guide for the proper therapeutic doses of atropine. Toxic effects of inadvertent overdose may be avoided by starting therapy with atropine in the MED correlated to body weight as described for the various age groups. It appears advisable to increase this dose by steps of 20% until the desired therapeutic effect is obtained. The occasional occurrence of erythema does not necessarily indicate a toxic level since some of the cases had flushing at the MED.

Conclusions

The susceptibility of apparently healthy children of all age groups to atropine by oral and subcutaneous administration was studied in carefully controlled experiments on 129 children. The minimal effective dose (MED) of atropine was determined by its effect in suppressing sialorrhea elicited either mechanically by chewing gum and/or pharmacologically by subcutaneous injection of methacholine.

Variations in individual susceptibility to atropine are large in all age groups and independent of the route of administration (oral, hypodermic).

The average MED/kg. body weight following oral administration is somewhat smaller in infants of 1 to 12 months and children from 12 to 36 months (0.16 and 0.14 mg./kg., respectively) than in older children in the age groups of 3 to 6 years and 6 to 12 years (0.22 and 0.20 mg./kg., respectively). Comparable results are obtained by hypodermic administration.

The ratio between the MED by mouth and the MED by hypodermic injection is approximately 3:1 in all age groups.

The determination of the susceptibility of children of various ages to atropine fails to adduce evidence supporting the assumption of an increased resistance to atropine or of a physiologic vagotonia in infants.

The relation of the MED of atropine in apparently healthy children to the doses recom-

mended in pediatric therapy is discussed. The calculation of the dosage of atropine by body weight is recommended.

REFERENCES

1. Lust, F., Diagnostik und Therapie der Kinderkrankheiten, Berlin-Wien, Urban & Schwarzenberg, 1923.
2. Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, 1948, p. 2.
3. Goodman, L., and Gilman, A., Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 469.
4. Friedberg, E., Die Pharmakologische Funktionsprüfung des vegetativen Nervensystems im Kindesalter, Arch. f. Kinderh. **69**:1 and 107, 1921.
5. Ritte, F., Weitere Atropinstudien bei Kindern, Arch. f. Kinderh. **79**:89, 1926.
6. Lindberg, G., Studien ueber die Wirkung des Atropins beim gesunden und kranken Saeugling, Acta pediat. **4**:309, 1925.
7. White, P. J., Gastro-enterospasm as manifestation of autonomic imbalance in early infancy, Am. J. Dis. Child. **26**:91, 1923.
8. Benzing, R., Ueber Atropinfieber bei Saeuglingen, Monatschr. Kinderh. **24**:509, 1923.
9. Adolphe, E. F., Quantitative relations in physiological constitutions of mammals, Science **109**: 579, 1949.
10. Benedict, F. B., and Talbot, F. B., Metabolism and Growth from Birth to Puberty, Publication no. 302, Washington, D. C., Carnegie Institution of Washington, 1921.
11. Leigh, M. D., and Belton, M., Premedication in infants and children, Anesthesiology **7**:611, 1946.
12. Smith, R. M., Methods of induction in pediatric anesthesia, New England J. Med. **240**:761, 1949.
13. Munns, G. F., Atropine hyperpyrexia in early infancy, J. A. M. A. **93**:171, 1929.
14. Pilcher, J. D., Atropine tolerance in infants and children: Negative action of serum of tolerant subjects, J. Pharmacol. & Exper. Therap. **52**:196, 1934.
15. Willberg, M. A., Die natuerliche Resistenz einiger Tiere dem Atropin gegenueber, Biochem. Ztschr. **66**:389, 1914.
16. Schlossmann, H. A., Relationship between age and action of atropine and morphine, J. Pharmacol. & Exper. Therap. **60**:14, 1937.
17. Obata, T., Ueber die Beziehung der Toleranz der weissen Ratten gegen verschiedene Arzneimittel zu ihrem Lebensalter, Jap. J. M. Sc., IV, Pharmacol. **5**:83†, 1931.
18. Kanda, Z., Ueber die Beziehung zwischen dem Lebensalter und der Toleranz fuer Atropin bei weissen Ratten, Jap. J. M. Sc., IV, Pharmacol. **14**:13, 1941.

SPANISH ABSTRACT

La Dosis de Atropina en Infantes y Niños

La susceptibilidad a la atropina (oral o subcutanea) en niños aparentemente saludables fué estudiada cuidadosamente en un experimento controlado en 129 niños. La dosis minima efectiva (MED) fué determinada por el efecto de supresion de la sialorrea, usando como medio indicador el "chewing gum" o la injection subcutanea de methacolina.

Las variaciones individuales en la susceptibilidad a la atropina fueron grandes en todas las edades independientemente de la ruta de administracion.

El promedio de la MED/kg de peso de atropina por via oral fué un poco menor en niños de 1 a 12 meses y de 12 a 36 meses (0.16 60.4 mg/kg respectivamente) que en los niños mayores de edad 3 a 6 años y 6 a 12 anos (0.22 a 0.20 mg / kg respectivamente). Resultados comparables fueron obtenidos usando la via subcutanea.

La relacion entre la MED oral y la MED subcutanea es aproximamente 3:1 en todas las edades.

La determinacion de la susceptibilidad a la atropina en niños de diversas edades, no arrojó evidencia afirmativa de aumento de la resistencia a la droga ni tampoco de la presencia de una vagotonia en la infancia.

La relacion de la MED de atropina en niños aparentamente saludables y la dosis recomendada en la terapeutica pediatrica es discutida. Los autores recomiendan el uso del peso del paciente para el calculo de las dosis de atropina.

1853 West Polk Street

677 CONGENITALLY MALFORMED INFANTS AND ASSOCIATED GESTATIONAL CHARACTERISTICS

II. Parental Factors

By JANE WORCESTER, DR.P.H., STUART SHELTON STEVENSON, M.D., AND ROBERT GERALD RICE, M.D.
Boston

MATERNAL AGE

THE infants born with congenital defects in the Boston Lying-in Hospital during the period 1930-1941 have been studied in a general way in Part I of this paper.[1] The problems of classification of defects, fatality, annual and seasonal distribution have been discussed. In this section attention will be turned to parental factors. It was stated in the description of the material that during the period under study over 90% of the primiparous and approximately 50% of the multiparous women under the care of the hospital were delivered in the hospital. The remainder of the women were delivered in their homes. The defective infants born to this latter group were not included in this series since their records in general were inadequate. The hospital population is therefore weighted with first births.

The age distribution of the 29,024 women delivered in the hospital during the period under study was not tabulated, but a sample of 1000 is available which consists of the births in the hospital during March and April, 1931, September and October, 1932, and January and February, 1933.* The age distribution of mothers of all live births in Massachusetts, 1930-41, is also at hand. Table 1 gives the age distribution of mothers in Massachusetts, in the Boston Lying-in Hospital sample and in the group of defective infants. Comparison of the age distributions shows that those of Massachusetts mothers, of the hospital sample and of mothers of the surviving defective infants are very much alike. It is not possible to conclude, nevertheless, that mothers of surviving defective infants do not differ in age from mothers of live births in general, because the group of Massachusetts mothers may contain relatively few primiparae and because the sample of 1000 mothers delivered in the hospital was taken during the depression years. Mothers of infants dead at birth due to malformations, in contrast to those of surviving defective infants, are old.

Some pertinent questions may be raised on the basis of this evidence. Is it not possible that several observers[2,3] have suggested that maternal age is a factor in the etiology of congenital anomalies because, in an entirely laudable effort to obtain series of defective infants with confirmed diagnoses, their material thus has become heavily weighted by dead infants? In other words, may it not be that the age of the mother is of great importance in the survival of the infant but is of little or no significance in the etiology of congenital

From the Departments of Biostatistics and of Maternal and Child Health, Harvard School of Public Health, from the Boston Lying-in Hospital and from the Department of Obstetrics, Harvard Medical School, Boston.

(Received for publication Nov. 3, 1949.)

* The authors are indebted to Dr. Stewart H. Clifford for this sample of mothers.

TABLE 1

AGE DISTRIBUTION OF MOTHERS OF NORMAL AND OF MALFORMED INFANTS

Age (Yr.)	Massachusetts Mothers	BLiH Sample	Mothers of Malformed		
			Surviving Infants	Neonatal Deaths	Still-births
Under 20	6.2%	5.4%	7.4%	1.2%	7.5%
20–24	26.6	32.9	27.9	21.2	23.3
25–29	29.7	31.2	30.4	28.8	29.2
30–34	21.5	18.7	20.1	31.2	20.8
35–39	12.0	8.2	10.2	13.8	14.2
40–44	3.7	3.6	3.9	2.5	4.2
45 and over	.3	0	0	1.2	.8
Total	100.0	100.0	99.9	99.9	100.0
No.	781,585	1,000	283	80	120
Average* age	28.43	27.61	28.09	29.90	28.92

* These averages were computed from finer age distributions.

TABLE 2

NEONATAL AND STILLBIRTH RATES PER 100 FOR MALFORMED INFANTS

Maternal Age (yr.)	Defective Infants Born Alive			Neonatal Mortality Rate		
	Birth order		Total	Birth order		Total
	1	2 and over		1	2 and over	
Under 20	16	6	22	6.2%	0%	4.5%
20–29	111	94	205	15.3	24.5	19.5
30 and over	21	115	136	28.6	28.7	28.7
Total	148	215	363	16.2	26.0	22.0

Maternal Age (Yr.)	Total Defective Infants			Stillbirth Rates		
	Birth order		Total	Birth order		Total
	1	2 and over		1	2 and over	
Under 20	22	9	31	27.3%	33.3%	29.0%
20–29	140	128	268	20.7	26.6	23.5
30 and over	31	153	184	32.3	24.8	26.1
Total	193	290	483	23.3	25.9	24.8

anomalies? Or, again, is it perhaps true that age of the mother is related to the expressivity of the anomaly?

Study of the mortality in the defective infants serves to sharpen these questions. Table 2 gives the mortality rates and stillbirth rates according to the age of the mother for first and other births. The stillbirth rates show no consistent variation with the maternal age, but the neonatal mortality rates, although only a small number of deaths is involved, increase consistently as the mother's age increases. Inclusion of the group with invalid diagnoses would not have changed the trend. This shows in another way that mothers of defective infants dying under 10 days tend to be older than mothers of defective infants who survive. Yerushalmy[4] studied the neonatal (deaths under 1 month of age) mortality of New York State, exclusive of New York City, for 1936 in relation to order of birth

TABLE 3

BIRTH ORDER OF NORMAL AND OF MALFORMED INFANTS

Birth Order	BLiH Sample	Malformed Infants		
		Surviving Infants	Neonatal Deaths	Still-births
1	42.8%	43.8%	30.0%	37.5%
2	22.6	25.4	30.0	20.0
3	13.2	7.4	15.0	13.3
4	8.1	8.5	10.0	9.2
5	4.1	4.6	3.8	3.3
6	2.9	3.9	2.5	5.0
7	2.3	2.5	2.5	3.3
8	1.3	1.8	1.2	2.5
9	1.3	.7	1.2	2.5
10 and over	1.4	1.4	3.8	3.3
Total	100.0	100.0	100.0	99.9
No.	1,000	283	80	120

and age of the parents. The neonatal mortality of full term births showed the same type of variation with age of the mother as is shown by this group of defective infants.

Table 3 gives the birth orders of the malformed infants and of the sample of 1000 babies delivered in the hospital. The birth order of Massachusetts infants is not available since this item of information is not included on the birth certificate in this state. This table shows the same type of variation in birth order as was shown in table 1 for maternal age. Defective surviving infants and the Boston Lying-in Hospital sample have the same distribution. Neonatal deaths due to anomalies and stillbirths, on the other hand, have higher birth orders.

When this study was planned, it was decided to abstract and study the records of the defective infants and their mothers and on the basis of the information thus obtained to select a control series from the 29,024 hospital births. However, a considerable amount of information was found to be available in the annual reports of the Boston Lying-in Hospital. It was found that a control series was needed from which the neonatal mortality and stillbirth rates for nonmalformed infants could be computed simultaneously according to age of mother, birth order of baby, prematurity and other factors. It was

TABLE 4

History of Mothers Giving Birth to 2 Malformed Infants and Data Concerning Their Infants

Mother	Birth Order	Yr. of Birth	Status of Infant	Defect	Maternal History
A.H.	*6*	1932 (BLiH)	Stillborn	Anencephalus	Bleeding, 6th mo.; polyhydramnios
	5	1930 (BLiH)	Stillborn	Anencephalus	No significant history
	4	1930 (BLiH)	Survived	None	No significant history
	3	1928	Survived	No history	
	2	1925	Survived	No history	
	1	1923	Survived	No history	
A.P.	*4*	1936 (BLiH)	Survived	Bilateral, clubbed feet, Subluxation of wrists	Chronic R.H.D.
	3	1934 (BLiH)	Stillborn	Hydrocephalus, Achondroplasia	Chronic R.H.D. Polyhydramnios
	2	1929 (BLiH)	Survived	No defect	Chronic R.H.D.
	1	1928 (BLiH)	Survived	No defect	Chronic R.H.D.
M.S.	*3*	1933 (BLiH)	Stillborn	Hydrocephalus	Question of fibroid
	2	1932 (BLiH)	Stillborn	Anencephalus, Spina bifida	No significant history
	1	1931	Stillborn	No history	
D.L.	*2*	1935 (BLiH)	Neonatal death	Anomalies of skull, brain, legs and feet	Bleeding, 8th mo.
	1	1933 (BLiH)	Survived	Hypospadias	Respiratory infection, 8th mo.
M.L.	*7*	1935 (BLiH)	Survived	Hydrocephalus, Spina bifida	No significant history
	6	1933 (BLiH)	Survived	Hydrocephalus meningocele, Spina bifida	No significant history
	?	1928	Survived	No history	
	?	1923	Survived	No history	
	?, ?, ?	?	3 miscarriages	No history	
C.A.	*2*	1935 (BLiH)	Stillborn	C.H.D., Multiple ovarian cysts	Pre-eclampsia, 8th mo.
	1 (Twins)	1933 (BLiH)	(a) Stillborn	Mesenteric cyst	Bleeding, 7th mo. Bleeding, 3rd and 4th mo.
			(b) Neonatal death, cerebral hemorrhage	No defect	Paroxysmal tachycardia
D.Z.	*3*	1935 (BLiH)	Stillborn	Anencephalus, Spina bifida	Question of toxemia, 9th mo.; polyhydramnios
	2	1935 (BLiH)	Stillborn	Anencephalus	Respiratory infection, 9th mo.; polyhydramnios
	1	1932	Survived	No history	
M.H.	*4*	1941 (BLiH)	Stillborn	Hydrocephalus, Clubbed foot, Accessory spleen	Hgb. 55%, 8th mo.
	3	1940 (BLiH)	Survived	None	No significant history
	2	1938 (BLiH)	Stillborn	Hydrocephalus	No significant history
	1	1935 (BLiH)	Survived	None	No significant history
A.B.	*4*	1938 (BLiH)	Neonatal death	Microgyria, Microcephaly, Interauricular defect, Hypoplastic kidney, Hypertrophy of adrenals, Clubbed feet, Polydactylism, Syndactylism	No significant history
	3	1937 (BLiH)	Neonatal death	C.H.D., Absent gallbladder, Hypoplastic kidney, Clubbed feet, Polydactylism, Syndactylism	No significant history
	2	1935 (BLiH)	Survived	No defect	Toxemia
	1	1932 (BLiH)	Neonatal death Cerebral hemorrhage	No defect	No significant history
M.R.	*3*	1940 (BLiH)	Survived	Webbed fingers and toes	No significant history
	2	1936 (BLiH)	Survived	Mongolism, Questionable C.H.D., Intestinal obstruction	Questionable heart disease
	1	1934	Survived	No history	
M.P.	*2*	1940 (BLiH)	Survived	C.H.D., Pigmented naevus of head	No significant history
	1	1938 (BLiH)	Stillborn	Anencephalus	Polyhydramnios

felt that such questions could not be answered from a sample of the births and that analysis of the entire 29,024 would be necessary to discuss them adequately. This was not feasible. Consequently, it is suggested that in conjunction with current studies of congenitally malformed infants from the records of maternity hospitals, complete analysis of all neonatal deaths, stillbirths and surviving infants be made. Only from such a study will it be possible to determine whether the mother's age is related to etiology of congenital anomalies or merely, as seems likely, to the survival of the infant.

Age of the mother was studied in relation to the type of defect. Both methods of classifying the defects, system affected and month during gestation were used. No consistent differences for any group of infants appeared except for mongolism which deserves special mention. Mothers of mongoloid infants consistently have been found to be old.[5] They are, indeed, the oldest group of mothers in this series (33.1 yr.) when only those groups with more than 10 cases, as given in table 2 of Part I of this article,[1] are considered.

Other factors of the same type as age of mother have been studied. Paternal age behaves in the same way as maternal age except that the fathers are, on the average, three years older than the mothers. Other variables which showed no consistent differences when one type of anomaly was compared with another were age at marriage, number of years since the last pregnancy, the number of years since marriage and the interval between births.

Previous Pregnancies

It was stated in the introduction that 11 of the mothers in this series each gave birth to two malformed babies in the Boston Lying-in Hospital. Table 4 gives the pregnancy history of these 11 mothers. It is interesting to note that the type of defect was repeated in five instances and that in the other six cases the mothers gave birth to infants whose defects differed widely.

While 11 is a very small number for the computation of rates, the rates involving this number are none-the-less important since they indicate the frequency with which malformed children appeared among the previous pregnancies. Four hundred seventy-two mothers gave birth to 120 stillborn, malformed infants, 80 malformed infants who died under 10 days and 283 surviving infants with valid diagnoses. Previous to the birth of the last malformed child born to them during the period 1930-1941 (the index case), these 472 mothers experienced 802 pregnancies. The results of 32 of these are unknown; 113 of them ended in abortion or miscarriage. The abortion rate in this group previous to the birth of the malformed child is 15%. This figure, which cannot be considered to

TABLE 5

Rates of Previous Birth of Malformed Children

Index Case	Previous Malformed Infant	Previous BLiH Births	Rate/100
Surviving infant	4	143	2.8%
Neonatal death	2	39	5.1
Stillbirth	5	48	10.4
Total	11	230	4.8

be well determined, was approximately the same whether the index case was a stillbirth, a neonatal death or a surviving infant.

There remain 657 pregnancies resulting in a stillborn or live infant; 230 of these were delivered in the Boston Lying-in Hospital. The records of these 230 births were abstracted and the rate of previous birth of malformed children is based on this number. Table 5 gives these rates.

It has been stated that the numbers involved in these computations are very small. Approximately 5% of the births, previous to that of the malformed child, were defective infants. The rate of births of malformed infants with confirmed diagnoses in the entire hospital population was shown in table 7 of Part I[1] to be 1.7%. When the index case was a stillbirth due to anomalies, 10% of the previous births resulted in defective infants. Table 4 indicates that this 10% was made up of stillborn infants with defects of the central nervous system. These results in conjunction with those of others do not contradict the suggestion that the defects which repeat may be those of the central nervous system which generally result in stillbirth.[2, 6, 7]

TABLE 6

COMPLICATIONS OF 483 PREGNANCIES

Complication	No. of Pregnancies with Complication	Percentage with Complication
Polyhydramnios	50	10.4%
Febrile illness		
1st trimester	5	1.0
2nd and/or 3rd trimester	60	12.4
Chronic illness	48	9.9
Vomiting	25	5.2
Toxemia	65	13.5
Threatened abortion	63	13.0
Gynecologic complications	62	12.8

COMPLICATIONS OF PREGNANCY

Table 6 presents seven complications of pregnancy concerning which data were available for all of the mothers in the series. Mothers of twins and of the 174 infants with questionable diagnosis of defect are not tabulated here.

Unfortunately, no adequate control group is available for comparison with this series. It has been stated that such a control group would have to have been selected from the hospital records with due consideration for such factors as month and year of birth, status of infant, birth order, prematurity and maternal age, etc. It would ultimately have involved analysis of the information relating to the 29,024 births, a prodigious undertaking. Such analysis of current material is feasible and should be profitable. In the present study it has been possible in some instances to use series collected for other purposes as controls and in other instances to make comparisons within the group of malformed infants.

Polyhydramnios: 10.4% of the mothers were diagnosed as suffering from polyhydramnios. In the group of 65 anencephalic infants, however, there were 33 instances of polyhydramnios, a rate of 51%. It is thus evident that the frequency of this complication of pregnancy is negligible except where the pregnancy results in an anencephalic infant. Other observers[8] found that polyhydramnios complicated 20 out of 87 (23%) preg-

nancies which resulted in infants with tracheo-esophageal fistula. There were only four infants with this defect in the present series.

Febrile Illness: Only 1.0% of the mothers gave a history of a febrile illness (usually described as an upper respiratory infection) during the first trimester of pregnancy. Although this might imply that infectious disease is not important as a teratogenic agent, it seems more plausible to believe that the average pregnant woman is unable to recall minor illnesses which afflicted her at a time when she may not even have known that she was pregnant. From such a viewpoint, the limitations of questionnaires are apparent.

A history of febrile illness at some time during the last two trimesters of pregnancy and therefore during a period when most of them were under observation was given by 12.4% of the mothers; most of these illnesses were upper respiratory or urinary tract infections. This rate does not seem unduly high and since the infections occurred at a time when the fetus's organogenetic period was finished they would not be expected to result in his malformation. However, six of the mothers of the 11 surviving infants with congenital hydrocephalus as a single defect had illnesses late in pregnancy (three upper respiratory, two urinary, one gonococcal infections). This is of interest because it has long been known that congenital, internal hydrocephalus results from obliteration of the foramen of Magendie such as may result from infection: syphilis and toxoplasmosis are currently accepted as causative agents. Other infections, occurring late in pregnancy, may be important in the etiology of hydrocephalus where this occurs as an isolated defect.

Chronic Illness: 9.9% of the mothers gave a history of chronic illness. This rate is not unusual; approximately 7% of it may be accounted for by all types of heart disease, mild or severe. It should be noted, however, that 10 of the 48 mothers who gave birth to infants with multiple anomalies (21%) gave a history of chronic illness.

Two and seven-tenths per cent (18 of 673) of all the mothers in the series had severe heart disease, most of it rheumatic. This does not differ from the rate recorded for all women cared for by the Boston Lying-in Hospital during the period under consideration. Since mothers with heart disease were in general delivered in the hospital, this percentage may be high compared with that of the whole population. The malformed infants of these mothers showed no consistency in type of anomaly. Maternal heart disease does not appear to be an important factor in the etiology of congenital anomalies.

Only 6 of 673 (0.9%) of all the mothers had diabetes mellitus and the anomalies in their infants were varied. This is a lower figure than was expected, but it is believed that the present sample is not valid because many diabetic women, followed in the various diabetic clinics of Boston, were not delivered at the Boston Lying-in Hospital. No conclusions may be drawn from this percentage and it is included merely to stress again the care which is needed in selecting samples for this type of study.

Vomiting: 5.2% of the mothers vomited with sufficient frequency during pregnancy to merit note of it on their records; the incidence did not increase with increasing maternal age. Stander[9] estimates that 50% of women vomit at some time during the first 6 to 12 weeks of pregnancy but that only 1 out of every 150 pregnant women vomit excessively. Although 5.2% seems therefore somewhat high, it is difficult to find an adequate control group for comparison. Because of this, and because most of the vomiting occurred after the fetal organogenetic period was finished, it is not possible to conclude from this series that vomiting during pregnancy is teratogenic. It is worth noting, however, that 8 of 70 (11.4%) of the women giving birth to infants with cardiac defects and 7 of 48 (14.6%) of the women bearing infants with multiple anomalies were noted as suffering from vomiting.

Toxemia: 13.5% of the mothers were classified as toxemic, according to the definition of the Boston Lying-in Hospital. The frequency increased with increasing maternal age, being 11% for mothers under 30 years of age (34 of 299) and 17% for older mothers (31 of 184). The general incidence of toxemia in this hospital at this time and similarly defined was approximately 10%. Although it should again be noted that 12 of 70 (17%) of the women giving birth to infants with cardiac defects and 9 of 48 (19%) of the women bearing infants with multiple anomalies were classified as toxemic, it is impossible to conclude from this series that toxemia is teratogenic.

Threatened Abortion: 13% of the mothers gave a history of threatened abortion (prenatal bleeding) and the rate was not affected by maternal age. An adequate control group for comparison is again difficult to find, but this percentage seems high and was especially

TABLE 7

CERTAIN COMPLICATIONS OF PREGNANCY TABULATED ACCORDING TO FATE OF INFANT

Complication	283 Surviving Infants		80 Neonatal Deaths		120 Stillbirths	
	No. of Mothers with Comps.	Percentage with Comps.	No. of Mothers with Comps.	Percentage with Comps.	No. of Mothers with Comps.	Percentage with Comps.
Chronic Illness	27	9.5%	12	15.0%	9	7.5%
Vomiting	13	4.6	9	11.2	3	2.5
Toxemia	33	11.7	15	18.8	17	14.2
Threatened Abortion	26	9.2	13	16.2	24	20.0

high among the mothers of multiply malformed infants, amounting to 12 of 48 (25%). Most of the bleeding occurred in the first and second months of pregnancy. Prenatal bleeding seems worthy of further investigation as a factor of possible importance in the etiology of congenital anomalies.

Gynecologic Complications: 12.8% of the mothers exhibited gynecologic complications. These were a heterogeneous group, composed in the main of chronic leucorrhea and cervical tears. The rate is not high and the group is too mixed to warrant further discussion.

Table 7 presents certain complications of pregnancy tabulated according to the fate of the infant. Mothers of twins and of the 174 infants with questionable diagnosis of defect are again not listed.

Table 7 shows the increased association of certain complications of pregnancy with infants dying in the neonatal period. This does not at all imply these are important factors in the etiology of congenital anomalies. The series is presented, on the contrary, to emphasize that these complications frequently may be found high when a sample of dead malformed infants and their mothers is studied. It is obvious that this may lead to fallacious conclusions.

Placentas: 61% of the records (297 of 483) contained no data on placentas. Inspection indicated that the placentas which were examined represented a random sample within the series, except for the stillbirths whose placentas were examined almost routinely. The percentage of abnormal placentas among these stillbirths, however, did not differ appreciably from that for the total series. Table 8 shows that 31.2% of the placentas

TABLE 8

PLACENTAS

Series	No.	No. Abnormal	Percentage Abnormal
Defective	186	58	31.2%
Normal	64	17	26.6

which were examined grossly and microscopically were classified as abnormal by the present writers, who are not pathologists: their interpretations of the pathologists' reports are resultantly somewhat arbitrary. "Immature" placentas, unless some other defect was noted, were categorized as normal. A control series of placentas, obtained from a random sample of normal infants born in the Boston Lying-in Hospital during the period under study, shows that 26.6% were classified as abnormal. Numbers are small and the difference is negligible. The percentage of abnormal placentas in the series of defective infants, furthermore, did not vary greatly when related to type of defect or to fate of the infant. It increased with increasing age of the mother: 25 of 99 (25%) placentas of mothers

TABLE 9

MATERNAL HEMOGLOBIN LEVELS

Hemoglobin Level	No. of Mothers	Percentage of Mothers
Less than 75%	91	39.4%
Less than 65%	29	12.6

under 30 years of age were considered abnormal as compared with 33 of 87 (38%) placentas of older mothers. This may well be related to the increased frequency of toxemia with increasing age.

"Immature" placentas have been classified as normal because they relate directly to premature infants and the latter are frequent in the series as will be shown below; studies which attempt to correlate abnormal placentas with malformed infants must bear these facts in mind. No conclusion is possible from the small series presented here, but it would seem that the human placenta has a large margin of safety, as evidenced by the infarctions found almost routinely in placentas from normal pregnancies. It seems unlikely that faulty placentation as such is a frequent cause of congenital malformations. (The question of implantation has not been considered.)

Hemoglobin: Hemoglobin determinations were done routinely on patients in the Boston Lying-in Hospital only during the last three years of the period covered by the present series, and earlier occasional determinations cannot be used here because they were usually indicated by symptoms of anemia in the mother. Hemoglobin levels are recorded, however, for 231 of the 234 mothers who bore malformed infants during the years 1939, 1940 and 1941; these are presented in table 9. The Sahli method was used and the results were given as percentages of normal. The times of determination varied, but most readings were taken between the third and sixth months of pregnancy; this minimizes the effect of blood dilution in the latter months.

It will be noted that 39.4% of the mothers had hemoglobin levels lower than 75% and 12.6% of them had levels lower than 65%. The incidence of anemia is thus notably

greater than Stander[9] considers physiologic during pregnancy. This is of interest in view of the possible role of anoxia as a teratogenic agent. Numbers involved here are too small for further analysis and there is no adequate control. It is suggested, nevertheless, that hemoglobin determinations should be performed routinely in prenatal clinics and that the role of maternal anemia in the etiology of congenital anomalies should be more thoroughly studied in the future.

Prematurity

Table 10 shows that 26.5% of the malformed infants, exclusive of twins and the 174 babies with a questionable diagnosis of defect, weighed less than 2.4 kg. at birth and that 21.7% of them weighed less than 2.3 kg. This contrasts markedly with data obtained from a sample of infants, born in the Boston Lying-in Hospital during the same period,

TABLE 10

Prematurity

Series	No. of babies	Percentage of babies under 2.4 kg.	Percentage of babies under 2.3 kg.	Percentage of babies born more than 17 days early
Malformed surviving infants	283	12.0%	7.4%	12.7%
Malformed infants dying under 10 days	80	32.5	25.0	30.0
Malformed infants stillborn	120	56.7	53.3	52.5
Total malformed infants	483	26.5	21.7	25.5
Total normal infants	225	5.3	3.6	5.8

in which 5.3% weighed less than 2.4 kg. at birth and 3.6% weighed less than 2.3 kg. The table shows, furthermore, that 25.5% of the defective infants were born more than 17 days previous to their mothers' expected dates of confinement, as compared to 5.8% of similarly early-born in the control group. It will be noted that many of the stillbirths and neonatal deaths due to anomalies were premature. Even among surviving infants, however, there is a strikingly increased frequency of premature babies as compared to the control series.* It is concluded that prematurity occurs more often in malformed infants; in many instances it probably results from the anomaly. All premature babies should be carefully examined therefore for evidences of congenital defects. They should be divided into malformed and normal groups when studies of morbidity and mortality are made concerning them.

Among the 174 infants removed from this table because of questionable validity of diagnosis, it is interesting that there were 46 babies diagnosed as having "congenital heart disease" merely on the basis of a cardiac murmur. Six of 46 (13%) of these infants weighed less than 2.4 kg. and 13 of 46 (28%) were born more than 17 days previous to their mothers' expected dates of confinement. It is suggested that normal fetal blood channels may not yet be obliterated at the time of birth of a premature infant

* The increased frequency of prematurity in this series of defective infants is not due to the fact that the series may be weighted by first births.

and that the diagnosis of congenital heart disease in this group, on the basis of a cardiac murmur only, should be made with caution.

Summary

The obstetric records of all mothers who gave birth to congenitally malformed infants live or stillborn in the Boston Lying-in Hospital during the years 1930 through 1941, together with the pediatric records of their live babies during the neonatal period, have been abstracted and analyzed. Statistical evaluation of data from such a source offers a means to study the etiology of congenital anomalies; and many factors have been found to be associated with pregnancies which result in the birth of defective infants. The statistical method presents several difficulties, however, and it must be used with careful regard for proper sampling and controls, if fallacious conclusions are to be avoided. It is suggested that in future studies from large maternity hospitals analysis of all neonatal deaths and stillbirths be made in conjunction with analysis of defective infants. Such analysis of current records both of malformed and of normal infants should serve eventually to clarify the relations between the factors and to indicate which are the causes and which the effects.

Conclusions

During a 12 year period, 29,024 infants were born in the Boston Lying-in Hospital and 677 of these were described as defective; 483 of these had valid diagnoses, giving a rate of 1.7%. Malformed infants accounted for 15.9% of the total stillbirths and 13.2% of the total neonatal deaths. Thirty-two per cent of the malformed neonatal deaths had defects referable to the cardiovascular system and 27% had multiple deformities. Seventy-nine per cent of the malformed stillbirths had defects of the central nervous system.

Twinning occurred with approximately twice the expected frequency. Since twinning in itself may represent an anomaly or may be found with anomalies, it might prove instructive to explore environmental circumstances associated with an unusual frequency of twinning in a larger series.

Defects which appeared in the early months of gestation, or which presumably required more than one month for their formation, caused the highest neonatal mortality. Approximately one third of the infants had defects which required more than one month for their formation.

The total anomaly rate was significantly high in 1935 when births of defective infants reached a peak seven months after a widespread epidemic of rubella. These data were recorded before the teratogenic properties of this disease were suspected and are not subject to the bias which may complicate information currently being gathered. They suggest the relationship between rubella and congenital anomalies. This material offers, furthermore, a method of attack on the problem of congenital anomalies which can be used more effectively than it has in the past.

The number of births of infants whose anomalies presumably required more than one month for their development was consistently high in the third and fourth quarters of the year. This dates their conceptions and organogenetic periods in the fourth and first quarters of the year, a time when respiratory diseases are common. Speculation as to possible association is not prudent, but these results are of sufficient interest to suggest that an attempt should be made to confirm them.

With the exception of mothers of mongoloid infants, who are older, the age distribution of the mothers of surviving defective infants corresponds closely with that of

mothers of all live births in Massachusetts during 1930-1941 and with that of a sample of 1000 mothers delivered in the Boston Lying-in Hospital. Because of the nature of the control groups, however, it is not possible to conclude that mothers of surviving malformed infants do not differ in age from mothers of live births in general.

Mothers of malformed infants dying under 10 days of age were significantly older than mothers of surviving defective infants and the neonatal mortality of normal infants shows the same association with advanced maternal age. Thus, the age of the mother appears to be of importance in the survival of the infant but may have little significance in the etiology of congenital malformations. It is possible that several observers have suggested age as a teratogenic factor because, in an attempt to obtain series of defective infants with confirmed diagnoses, their material has thus become heavily weighted by dead babies.

Only 11 mothers in this series gave birth to two malformed infants in the Boston Lying-in Hospital. The rate of previous births of malformed infants to mothers in this series was 4.8%. The rate for the entire hospital population was 1.7%.

Polyhydramnios occurred in 10% of the pregnancies. Sixty per cent of these resulted in anencephalic infants. The frequency of polyhydramnios is thus negligible in this series except when the pregnancy results in anencephaly.

Only 1% of mothers gave a history of febrile illness in the first trimester of pregnancy. It seems probable that the average pregnant woman is unable to recall minor illnesses which afflicted her at a time when she may not even have known that she was pregnant. From such a viewpoint, the limitations of questionnaires are apparent.

A history of febrile illness at some time during the last two trimesters of pregnancy was given by 12.4% of the mothers. However, six of the mothers of the 11 surviving infants with congenital hydrocephalus as a single defect had illnesses late in pregnancy. It is suggested that maternal infections other than syphilis and toxoplasmosis may be important in the etiology of hydrocephalus where this occurs as an isolated defect.

Twenty-one per cent of mothers who gave birth to infants with multiple anomalies suffered from chronic illness, as compared to 9.9% of the mothers in the total series.

The frequency of severe maternal heart disease was not unusual, the sampling seems valid, and maternal heart disease does not appear to be an important factor in the etiology of congenital anomalies.

Eleven and five-tenths per cent of mothers who gave birth to infants with congenital heart disease and 14.6% of mothers bearing infants with multiple anomalies vomited with sufficient frequency to merit note of it in their records. This contrasts with a rate of 5.2% for mothers in the total series.

Thirteen and five-tenths per cent of mothers were classified as toxemic, a rate which does not differ significantly from the rate for mothers of normal infants. It contrasts, however, with a rate of 17% for mothers bearing infants with congenital heart disease and 19% for mothers who gave birth to infants with multiple anomalies.

Thirteen per cent of mothers gave a history of threatened abortion. This rate seems high and among mothers of multiply malformed infants it reached 25%. Further investigation is necessary to determine whether prenatal bleeding is a cause or an effect of malformation.

Chronic illness, vomiting, toxemia and threatened abortion are found with increased frequency as complications of pregnancy in those women bearing defective infants dying in the neonatal period. Thus, they may be found often when a sample of dead malformed

infants and their mothers is studied. This may lead to fallacious conclusions.

Placentas in this series were not more frequently abnormal than in a control group of pregnancies, and it seems unlikely that faulty placentation as such is a frequent cause of congenital anomalies.

Thirty-nine and four-tenths per cent of the mothers had hemoglobin levels below 75%. This frequency of anemia is greater than can be considered physiologic and is of interest in view of the possible role of anoxia as a teratogenic agent. Hemoglobin determinations should be performed routinely in prenatal clinics and the role of maternal anemia in the etiology of congenital anomalies should be studied more thoroughly.

Twenty-six and five-tenths per cent of the infants weighed less than 2.4 kg. and 25.5% of them were born more than 17 days previous to their mothers' expected dates of confinement. These rates are significantly high and it may be concluded that prematurity occurs more often in malformed infants. All premature infants should be carefully examined, therefore, for evidences of congenital defects. They should be divided into malformed and normal groups when studies of mortality and morbidity are made concerning them.

(Part I of the article "677 Congenitally Malformed Infants and Associated Gestational Characteristics" appeared in the July issue of PEDIATRICS.*)*

REFERENCES

1. Stevenson, S. S., Worcester, Jane, and Rice, R. G., 677 congenitally malformed infants and associated gestational characteristics. I. General considerations, PEDIATRICS **6**:37, 1950.
2. Murphy, D. P., Congenital Malformations, ed. 2, Philadelphia, J. B. Lippincott Company, 1947.
3. Penrose, L. S., Maternal age, order of birth and developmental abnormalities, J. Ment. Sc. **85**:1141, 1939.
4. Yerushalmy, J., Neonatal mortality by order of birth and age of parents, Am. J. Hyg. **28**:244, 1938.
5. Bleyer, A., Role of advanced maternal age in causing mongolism: Study of 2,822 cases, Am. J. Dis. Child. **55**:79, 1938.
6. Quigley, J. K., Occurrence of anencephalic monsters in successive pregnancies, Am. J. Obst. & Gynec. **46**:879, 1943.
7. Dunn, H. G., and Salter, J. G., Recurrent anencephaly, J. Obst. & Gynaec. Brit. Emp. **51**:529, 1944.
8. Ingalls, T. H., and Prindle, R. A., Esophageal atresia with tracheoesophageal fistula, New England J. Med. **240**:987, 1949.
9. Stander, H. J., Williams Obstetrics, ed. 8, New York, D. Appleton-Century Company, 1941.

SPANISH ABSTRACT

Estudio de 677 Casos de Niños con Malformaciones Congenitas y de Sus Caracteristicas de Gestacion. I. Consideraciones Generales; II. Factores Maternos

Los autores hacen un sumario y analisis de las historias obstetricas de todas las madres que dieron a luz niños malformados, vivos o fallecidos, en el Boston Lying In Hospital entre los años 1930 a 1941 inclusive conjuntamente con la revision de las historias pediatricas durante el periodo neo-natal de los niños que sobrevivieron. La interpretacion estadistica de estos datos ofrece un medio para el estudio de la etiologia de las anomalias congenitas debido a la observacion de numerosos factores asociados con el embarazo que parecen influenciar el nacimiento de niños defectuosos. Este metodo estadistico presenta ciertas dificultades de interpretacion y debe utilizarse teniendo cuidado especial en la debida seleccion del material de observacion asi como de los controles, si se han de evitar falsas conclusiones. Se sugiere que en estudios futuros similares en los Hospitales de maternidad, este analisis de las muertes neo-natales y fetales (still born) se realize conjuntamente con el analisis de las historias de niños defectuosos. Ademas el analisis de las historias clinicas, tanto de los niños

malformados como de los niños normales debe servir en el futuro para aclarar la relacion entre los distintos factores, asi como determinar las causas y los efectos en la produccion de estas anomalias.

Durante un periodo de doce años, 29,024 niños, nacieron en el Boston Lying In hospital. De estos, 677 fueron clasificados como defectuosos, de los cuales 483 tenian un diagnostico definido, o sea 1.7% del total.

Del grupo total de niños con malformaciones congenitas 15.9% correspondian al grupo de muertes fetales y 13.2% al grupo de muertes neonatales. En 32% de los casos de este ultimo grupo los defectos congenitos fueron atribuibles al sistema cardiovascular y en 27% las anomalies fueron multiples. En 79% de los casos del primer grupo (muertes fetales) las anomalias fueron referibles al sistema nerviosos central.

La incidencia de gemelos fue doble de la frecuencia esperada. La incidencia de gemelos por si misma o asociada a otros defectos congenitos constituye una anomalia; el estudio en estos casos de las circumstancias ambientales maternas es de un gran interes instructivo.

Los defectos congenitos que aparecieron en los primeros meses de la gestacion fueron responsables por la alta mortalidad del periodo neonatal. De este grupo aproximadamente una tercera parte tuvieron defectos congenitos que requirieron mas de un mes para su formacion.

El total de anomalias congenitas fué significantemente alto en el año 1935 cuando la incidencia de niños malformados llegó a su maximo, siete meses después de una severa epidemia de rubella. Estos datos sugieren la relacion entre la rubella y la ocurrencia de anomalias congenitas.

El numero de nacimientos de niños cuyas anomalias necesitaban mas de un mes para su desarrollo, fué consistentemente alto en el tercero y cuarto trimestre del año lo cual fija la concepcion y el periodo organogenetico en el cuarto trimestre del año anterior o sea, el primer trimestre del año del parto. Es decir, la epoca del año en los Estados Unidos cuando las enfermedades respiratorias son mas comunes.

Con la excepcion de madres de niños mongoloides, la distribucion de edad de las madres de niños defectuosos que sobrevivieron, correspondio con la edad promedio de las madres con nacimientos vivos en el estado de Massachusetts en los años 1930 a 1941 y con la edad de un grupo de 1000 madres que dieron luz en el Boston Lying In Hospital. Debido a la diferencias de los grupos de comparacion (controles) fué imposible eliminar la relacion de edad entre las madres de niños malformados que sobrevivieron y la edad de las madres de niños normales en general. La edad de las madres de niños malformados que murieron de menos de 10 dias de edad fueron significantemente mayor que la edad de las madres de niños defectuosos que sobrevivieron. Las muertes neonatales de niños normales tuvo la misma relacion con el aumento de edad de la madre. Aparentemente la edad de la madre juega un papel importante en la sobrevivencia del niño, aunque de poca significancia en la etiologia de las malformaciones congenitas.

Solamente 11 madres en esta serie dieron a luz dos veces a niños malformados. El promedio de nacimientos anteriores de niños malformados en relacion con las madres en esta serie fué 4.8. El promedio para todo el hospital fue 1.7%.

Polyhydramnios occurió en 10% de los embarazos y 60% de estos embarazos resultaron en niños anencefalicos. La frequencia de polyhydramnios fue neglegible en esta serie a excepcion hecha cuando el embarazo resultó en anencefalia.

Solamente 1% de las madres tuvieron historia de fiebre en el primer trimerse de gestacion. Sin embargo parece probable que el promedio de las mujeres embarazadas no logren recordar enfermades ligeras que ocurieron cuando ni siquiera sabian que estaban embarazadas.

En 2.4% de los madres se observaron historias anteriores de enfermedades febriles en alguna epoca durante los últimos dos trimestres de la gestacion. En seis de las madres de 11 niños que sobrevivieron una hidrocefalia como defecto unico, desarollaron enfermedad febril en la parte final del embarazo. Esto sugiere que otras infectiones maternas, además de la sifilis y de la toxoplasmosis, pueden tener importancia en la etiologia de la hidrocefalia cuando esta se presenta como defecto aislado.

En 21% de madres que tuvieron niños con anomalias multiples sufrieron de enfermedades cronicas, en comparacion con el 9.9% de enfermedades cronicas en el grupo de la serie total. La frequencia de enfermedades de corazon en las madres no parece ser un factor de importancia en la etiologia de anomalias congenitas. En 11.5% de las madres que tuvieron niños con enfermedad congenita de corazon y 14.6% de las madres que tuvieron niños con anomalias multiples tuvieron "vomitos" frequentemente durante el embarazo. Esto establece un contraste con el promedio de

vomitos de 5.2% de la serie total. La incidencia de toxemia del embarazo fue 13.5%; frequencia esta que no difiere significantemente de la ocurrencia de toxemia en las madres de niños normales. Sin embargo la frequencia de toxemia fué de 17% en las madres que tuvieron niños con enfermedad congenita de corazon y 19% en madres que tuvieron niños con anomalias multiples. El 13% de las madres tuvieron historias de principio de abortos. Esta incidencia de abortos fue mucha mas alta (25%) en las madres que tuvieron niños malformados.

Enfermedades cronicas, vómito, toxemia y principio de aborto son complicaciones frecuentemente encontradas en las madres embarazadas con niños congenitamente defectivos que fallecen el periodo neonatal.

Las placentas en esta serie de niños malformados no fueron mas abnormales que el grupo de control, siendo dudoso que los defectos de implantacion de la placenta sea una causa etiologica de anomalias congenitas.

En 39.4% de las madres la hemoglobina fue menos de 75%. Se discute la frequencia de esta anemia y de la posible significancia de la anoxia como agente teretogenico. Determinaciones de la hemoglobina deben hacerse rutinariamente en las clinicas prenatales y el role de la anemia materna en la etiologia de las malformaciones congenitas debe estudiarse mas intensamente.

En 26.5% de los niños malformados el peso al nacer fué menos de 2.4 kg y de ellos 25.5% nacieron prematuramente con mas de 17 dias. Esto es indicativo de que el nacimiento prematuro frecuentemente ocurre asociado con niños malformados. Por eso todos los prematuros deben examinarse cuidadosamente por posibles defectos congenitos. En el estudio de la mortalidad y morbilidad del prematuro, estos deben dividirse en dos grupos: prematuros normales y prematuros malformados.

55 Shattuck Street

CLOSING OF THE ANTERIOR FONTANELLE

By MILTON R. AISENSON, M.D.
Flushing, N.Y.

CURRENT pediatric textbooks differ in statements about the age at which the anterior fontanelle closes normally. Brenneman[1] states that "the anterior fontanelle should be closed by 15 months or earlier" and "closure . . . in the first five or six months may occur normally." According to Mitchell and Nelson,[2] "closure should be complete by 18 months and often is by 12 months." Holt and McIntosh's 1940 text[3] gives 9 to 16 months as the usual limits, but their 1936 edition[4] gave 14 to 22 months.

These ages are also different from those given by Scammon.[5] He found only 4.5% of infants with closed fontanelle by the age of 12 months and 80% by 24 months. Search of the available subsequent literature disclosed only Zahorsky's[6] observations of 116 infants, admittedly a small sample.

Premature closure of the fontanelle may occur in microcephaly and craniostenosis, delayed closure in rickets, hydrocephalus, hypothyroidism and cleidocranial dysostosis. Since a definition of normal is essential to an interpretation of the abnormal, the present study was undertaken.

MATERIALS AND METHODS

Records were reviewed at 2 child health stations of the New York City Department of Health. Patients attend these clinics during infancy and the preschool years. Physical examinations are done routinely 4 times during the 1st yr., 3 times during the 2nd yr. and then twice a year. The children in this study were born between 1939 and 1948. They came from lower income groups, but were not indigent. Almost all were white, 2nd and 3rd generation American, largely of Italian extraction. Adequate vitamin supplements were usually started in the 1st mo. Almost all the infants received evaporated milk formulae from birth. In general, they were eating a variety of foods by the 6th mo., although individual physicians attending the health station differed in the age and order in which they recommended addition of these foods to the infants' diets.

Closure of the fontanelle was determined by palpation, during the periodic physical examination. To minimize errors due to inadequate observation, infants who had not been seen within 6 mo. before closure were eliminated; this would also eliminate those infants whose fontanelle was closed at the 1st examination.

Major disease was rare in these children, probably because sick children are treated elsewhere. When closure occurred before 10 mo. or after 18 mo., special search was made for evidence of nutritional, osseous or endocrine disorder. No abnormalities were found in the early (before 10 mo.) group. In the late closing (after 18 mo.) group, questionable rickets was noted on 2 charts, which were eliminated.

About half the records were eliminated because of inadequate attendance. Breast fed and Negro infants were too few in number to warrant separate consideration. The 1677 infants in this series constitute a fair sample of healthy New York City babies.

OBSERVATIONS

Table 1 lists the number of infants whose fontanelle closed at each month; chart 1 gives the same data in graphic form. The wide range, 4 months to 26 months, is apparent.

From the Department of Health, City of New York, Bureau of Child Health, Infant and Pre-School Division, New York City.

(Received for publication Dec. 5, 1949.)

TABLE 1

Age at Which Fontanelle Closed (mo.)	No. of Infants	Percentage of Fontanelles Closed (Cumulative)
4	1	0.06%
5	12	0.8%
6	32	2.7%
7	39	5.0%
8	44	7.6%
9	99	13.5%
10	111	21.6%
11	141	28.6%
12	218	41.6%
13	181	52.4%
14	121	60.0%
15	163	69.3%
16	156	78.6%
17	102	84.7%
18	111	91.3%
19	73	95.6%
20	42	98.2%
21	14	99.0%
22	8	99.4%
23	3	99.6%
24	5	99.9%
26	1	100.0%
Total no. of infants		1677
Mean age at which fontanelle closed		13.5 mo.
Modal age at which fontanelle closed		12 mo.
Lowest 5 percentile		4 to 7 mo.
Highest 5 percentile		19 to 26 mo.

By eliminating the lowest and highest five percentiles, 90% of closures occur between 7 and 19 months. Mean and mode are, respectively, 13.5 and 12 months. At one year of age, 41.6% of the infants had closed fontanelles, of which 2.6% occurred before 6 months.

The interval between examinations explains the irregularities in the curve, most marked at 14 months. This interval has also pushed the entire curve to the right, especially after 13 months.

Comment

It is clearly shown in the present study that there is a wide range in the age at which the anterior fontanelle closes with extremes at 4 and 26 months. If abnormal closing is suspected, this variation must be considered.

The large percentage of infants whose fontanelle was closed before the age of 1 year is of more interest. Abt's Pediatrics[5] states that 4.5% of fontanelles were closed at this time; the present study finds 41.6%. This suggests there may be a trend towards earlier closure

of the fontanelle. "Normal" standards do change; a familiar example is the father-son studies at several colleges. Although this may be due to evolutionary processes, it is tempting to try to explain it by nutritional changes, either generally or by a specific factor. Zahorsky[6] noted that the fontanelle was closed at 7 to 14 months in 83 infants on high protein diets, but not in 33 on low casein formulae or breast milk. They were not followed to determine the actual age of closure; all his patients were within the age

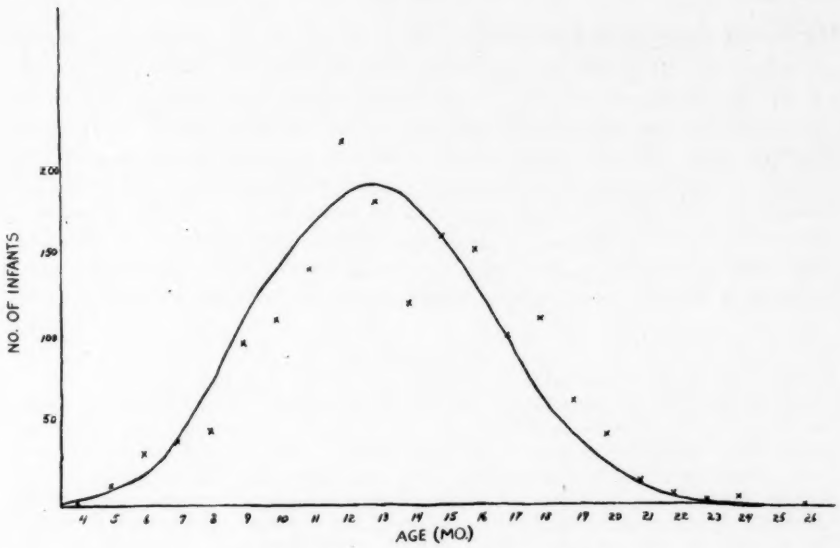

CHART 1. Age at which fontanelle was closed.

limits defined in the present paper. This question, as well as possible geographic and racial variations, can be answered only by further study of large numbers of infants.

SUMMARY

The age at which the anterior fontanelle closed in 1677 infants varied between 4 and 26 months, with 90% between 7 and 19 months. In the first year, 41.6% closed, of which 2.7% occurred by 6 months and 13.5% by 9 months. Compared to data in older textbooks, this suggests a trend towards earlier closure of the fontanelle.

REFERENCES

1. Brenneman, J., in Brenneman's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, 1948, vol. 1, chap. 19, p. 12.
2. Palmer, C. E., and Ciocco, A., in Mitchell-Nelson Textbook of Pediatrics, ed. 4, Philadelphia, W. B. Saunders Company, 1945, p. 29.
3. Holt's Diseases of Infancy and Childhood, ed. 11, revised by Holt, L. E., Jr., and McIntosh, R., New York, D. Appleton-Century Company, 1940, p. 30.
4. Ibid., ed. 10 revised, 1936, p. 25.
5. Scammon, R. E., in Abt's Pediatrics, Philadelphia, W. B. Saunders Company, 1923, chap. 3, p. 269.
6. Zahorsky, J., Some observations of anterior fontanelle, Arch. Pediat. **61**:259, 1944.

SPANISH ABSTRACT

Tiempo de Ocurrencia del Cierre de la Fontanella Anterior

La edad del cierre de la fontanella anterior en 1677 niños varió entre 4 y 26 meses de edad. En 90% de los casos el cierre occurió entre los 7 y los 19 meses de edad: con 41.6% cerrándose en el primer año, 2.6% a los 6 meses, y 13.5% a los 9 meses. Este estudio sugiere que el cierre de la fontanella anterior esta occufiendo actualmente mas tempranamente si se compara con observaciones mas antiguas.

144-16 72nd Avenue, Kew Garden Hills, N.Y.

PERTUSSIS DUE TO BRUCELLA BRONCHOSEPTICA

Case Report

By CHANG SHIH MAN, M.D.
Boston

THE close relation between the toxin and antigen of Br. bronchoseptica and H. pertussis was shown by Evans and Maitland.[1] Eldering and Kendrick[2] reported on the cultural characteristics and antigenic relation of H. pertussis, B. parapertussis and Br. bronchoseptica. Bradford[3] stated that H. influenzae, Br. bronchoseptica and B. parapertussis were capable of producing infection of the respiratory tract that closely resembled that caused by H. pertussis. Fairly extensive review of the literature, however, revealed no authentic case of pertussis caused by Br. bronchoseptica in human beings. Brown[4] isolated Br. bronchoseptica from a child with a mild pertussis-like picture but the hemopoietic and serologic response of his patient toward Br. bronchoseptica was not mentioned. The following is a case which the author believes to be pertussis caused by Br. bronchoseptica.

REPORT OF CASE

J. N., aged 2 yr., immunized against pertussis at 1 yr. of age and having no past history of pertussis, was admitted to South Department of the Boston City Hospital. History of sneezing rhinorrhea and gradually increasing coughing for 5 days was given. There was no known exposure to pertussis. Contact with dogs was intimate. Admission physical examination was negative. On admission WBC 22.9 thousand/cmm. with lymphocytes 72%. Nasopharyngeal culture, using Bordet-Gengou medium, revealed numerous pinhead-sized smooth entire glistening colonies with narrow zones of β hemolysis after 48 hr.' incubation. The colonies were formed by gram-negative coccobacilli agglutinated with H. pertussis antiserum to its titer of 1:640. The micro-organisms were reported as H. pertussis and the diagnosis of pertussis was made. Typical paroxysmal coughing by the patient was observed during the 1st 2 wk. of hospitalization. The frequency and severity of paroxysmal coughing decreased slowly thereafter. WBC showed a rise to 41 thousand on the 2nd hospital week. Nasopharyngeal culture made every 3rd day showed the same micro-organism repeatedly (called strain J.N. hereafter to facilitate further description). One month after admission, the patient was asymptomatic but nasopharyngeal culture was still positive for strain J.N. Patient was given aureomycin 2 gm./day for 5 days. Nasopharyngeal culture became negative for strain J.N. on and after the 4th day of treatment.

That strain J.N. was not H. pertussis was made evident by the sensitivity study to several antibiotics at Thorndike Memorial Laboratory on several strains of H. pertussis[5] and strain J.N. The results were tabulated in table 1 which compares the antibiotic sensitivity of strain J.N. to that of H. pertussis, strain M., tested simultaneously.

Further study on strain J.N. was made. It was actively motile. On first transfer from Bordet-Gengou medium, the freshly isolated organism grew well on blood agar, on eosin-methylene blue agar, in plain nutrient broth and in peptone water. It obviously required no X or V growth factors. It produced no acid or gas from dextrose, lactose, maltose, and saccharose. It reduced nitrate, formed no indole or hydrogen sulfide. It was agglutinated by Br. bronchoseptica antiserum up to a titer of 1:10,000. With the exception of its hemolytic activity, all findings were identical with those of a standard strain of Br.

From South Department, Boston City Hospital, Boston.
(Received for publication Dec. 10, 1949.)

TABLE 1

SENSITIVITY* OF BR. BRONCHOSEPTICA (STRAIN J.N.) AND H. PERTUSSIS (STRAIN M.) TO DIFFERENT ANTIBIOTICS

	Br. bronchoseptica strain J.N.	H. pertussis strain M.
Penicillin	400	1
Streptomycin	125	2.5
Aureomycin	10	0.31
Chloromycetin	10	0.63
Bacitracin	4000	62.5
Polymyxin	2.5	0.16
Aerosporin	10	0.16

* Sensitivity represents the minimal amount of antibiotic in μg./cc. Bordet-Gengou medium that inhibits growth completely after 72 hr.' incubation.

bronchoseptica obtained from American Type Collection, Washington, D.C. Based on those cultural and immunologic findings, strain J.N. was classified as Br. bronchoseptica. A subculture of strain J.N. was sent to and was classified as Br. bronchoseptica by Dr. Grace Eldering of the Michigan Department of Health. In addition to the findings described, Dr. Eldering showed that strain J.N. was agglutinated with parapertussis antiserum to its titer of 1:4,000, approximately one eighth of the titer with the homologous strain. With the particular H. pertussis antiserum she used, there was no agglutination of strain J.N. Inoculated intracerebrally into mice, the LD/50, as determined by her, varied around 500.

Agglutination tests were performed with the patient's sera using H. pertussis and strain J.N. as antigens. There was no agglutination of either antigen by sera obtained on the 19th, 25th, 32nd and 38th day after admission. Eight weeks after onset of illness, the patient's serum showed an agglutination titer of 1:256 against strain J.N. and no agglutination of H. pertussis.

The source of infection was not known. Several nose and throat cultures of patient's dogs failed to grow any Br. bronchoseptica.

SUMMARY

A case clinically resembling pertussis due to Br. bronchoseptica is reported.

REFERENCES

1. Evans, D. G., and Maitland, H. B., Toxin of Br. bronchoseptica and relationship of this organism to Hemophilus pertussis, J. Path. & Bact. **48**:67, 1939.
2. Eldering, G., and Kendrick, P. B., Parapertussis, J. Bact. **35**:561, 1938.
3. Bradford, W. L., in Textbook of Medicine, ed. 7, edited by R. L. Cecil, Philadelphia, W. B. Saunders Company, 1947.
4. Brown, J. H., Bacillus bronchisepticus infection in child with symptoms of pertussis, Bull. Johns Hopkins Hosp. **38**:147, 1926.
5. Wells, E. B., Shih Man, Chang, Jackson, G. G., and Finland, M., Antibiotic spectrum of hemophilus pertussis, J. Pediat. **36**:752, 1950.

SPANISH ABSTRACT

Tosferina Debida a la Brucella Bronchoseptica. Reporte de un Caso

Se reporta un caso clinicamente semejante a la tosferina en el cual el agente etiologico fué la brucella bronchoseptica.

745 *Massachusetts Avenue*

NEUROLOGIC LESIONS IN THE NEWLY BORN INFANT

I. Preliminary Study; II. Role of Prolonged Labor, Asphyxia and Delayed Respiration

By HADDOW M. KEITH, M.D., AND MILDRED A. NORVAL, M.D.
Rochester, Minn.

I. PRELIMINARY STUDY

LITTLE[1] in 1862 described the condition since known as "Little's disease." He ascribed this condition almost wholly to asphyxia of the nervous system of the infant as a result of some accident or process during birth. He gave the postmortem findings in only two cases, in one of which evidence of gross intracranial hemorrhage was found; in the other, only congestion of the whole brain was observed.

In 1885, McNutt[2] described the findings in 10 babies dying of birth injuries. In eight of these there was hemorrhage over the cortex and in two, at the base of the brain. She later reported a case of diplegia or Little's disease which she believed was due to a meningeal hemorrhage at birth. Her patient was shown, however, to have a hemorrhage that originated deep in the cortex and not in the superficial layers.

In the years since these reports were made, there have been many discussions about the relation between birth injury with resultant intracranial hemorrhage and spastic diplegia. Freud[3] wrote an extensive monograph in 1897, stating that he was unable to find evidence that diplegia was due to birth injury. He distinguished clearly between diplegia and double hemiplegia, the latter being due to gross hemorrhage, the former to a degenerative process. Collier,[4] in 1899, and again in 1924,[5] concluded that diplegia was due to neuronic degeneration, not to meningeal hemorrhage.

Weyhe,[6] in 1889, published the necropsy findings in 959 stillborn babies. In 122 of these (approximately 12%), he found intracranial hemorrhage. Other authors have reported series in which 20 to 65% of the patients had similar hemorrhages. In premature infants the percentage is even higher, Ylppö[7] claiming some degree of injury in 90% of his series of premature infants.

Beneke[8] showed in 1910, by means of a different technic at necropsy, that tears in the tentorium and falx are frequently the cause of birth hemorrhages. Seitz[9] showed that this type of injury occurred in half of his cases.

There have been a number of excellent reviews of the subject within the past two decades, notably by Ehrenfest,[10] Ford,[11] Craig,[12] McGuinness,[13] MacGregor[14] and Campbell.[15] Their work confirms previous observations in regard to the location of hemorrhages, and supplies data regarding numbers and causes of such lesions. Their studies were based chiefly on necropsy material.

As to asphyxia, there is some controversy as to whether cerebral asphyxia, or lack of

From the Section on Pediatrics, Mayo Clinic, Rochester, Minn.
These studies were carried out in co-operation with the Rochester Child Health Institute.
(Received for publication Oct. 20, 1949.)

oxygen alone, can cause permanent changes in the brain tissue with resulting clinical neurologic manifestations in childhood. Hannes,[16] in 1911, reported a study of three groups, each group composed of 150 children. Members of the first group had had asphyxia, those of the second had been subjected to versions or breech extractions, or both, and those of the third had been born by normal spontaneous deliveries. In each group there was an equal number of apparently abnormal, backward and defective children. Two idiots appeared in the second and third groups, and none in the first. Ford[11] stated that he could discover "No evidence that permanent injury may be produced by asphyxia due to oxygen deprivation." Fazekas and co-workers[17] and Smith[18] stated that it has been recognized for a long time that the fetus and the newborn infant can withstand greater degrees of anoxia than can the adult organism. McPhail and Hall[19] applied standard intelligence tests to 270 school children. They found that those children who had been apneic at birth did not show evidence of mental retardation when they reached school age.

On the other hand, Schreiber,[20] Lund[21] and Courville and Marsh[22] stated that neurologic disorders can result from permanent damage to the central nervous system caused by anoxia. Clifford[23] made a careful study of 11 babies born by cesarean section, who had been subjected to fetal anoxemia due to hemorrhage from a low-attached placenta. He stated that the clinical symptoms observed in these asphyxiated babies were the result of the changes due to anoxemia. Darke[24] stated that there are significant differences between the mental status of children who have been severely asphyxiated at birth and that of a control group of parents or siblings. He chose children who had been severely asphyxiated at birth and observed them during their school years. Windle,[25] in animal experiments, showed that asphyxia during birth could produce severe changes in the central nervous system and neurologic symptoms immediately after birth. However, the symptoms frequently were only transient. He stated that "not all asphyxiated human infants have permanent manifestations of nervous disease."

In Rochester, Minn., 95% of the babies in the city and surrounding country are born in St. Mary's Hospital which is staffed by members of the staff of the Mayo Clinic. Mothers are observed and receive care during the prepartum period, accurate records of deliveries are kept, the babies are cared for during the neonatal period, and by co-operation between the Rochester Child Health Institute and the Mayo Clinic, the development of a large percentage of the infants is followed for a number of years. We are attempting a long-term follow-up of patients in whom neurologic abnormalities may be present at birth, or in whom they occur in the early years of life. We are also interested in children in whom the possibility of physical injury by manipulation during delivery may occur, or in whom any evidence of prolonged labor or asphyxia of the infant may be present. It seemed to be of advantage to study a fairly large group for which there are available well-recorded observations of normal deliveries and normal infants, as well as abnormal or difficult deliveries and abnormal infants.

Incidence and Cause of Neurologic Lesions in the Newly Born Infant

During the years 1944 through 1947, there were 4,411 deliveries on the obstetric service at St. Mary's Hospital, with 4,464 total births. It was of interest that 57 (1.3%) of these infants had lesions, clinical or pathologic, which affected the nervous system primarily and which were evident during the neonatal period (approximately two weeks).

TABLE 1

DATA ON 12 INFANTS WHO DIED DURING 1ST WK. OF LIFE

Lived	Diagnosis	Clinical Cause of Death	Diagnosis at Necropsy
5 min.	Anencephaly	Anencephaly	Anencephaly
10 min.	Multiple congenital anomalies, exstrophy of bladder, hydrocephalus meningocele	Multiple congenital anomalies, exstrophy of bladder, hydrocephalus meningocele	Multiple congenital anomalies, nonexpansion of lungs
10 min.	Anencephaly, prematurity	Anencephaly, prematurity	Anencephaly, prematurity, craniorachischisis
60 min.	Atelectasis, club feet, hepatomegaly	Atelectasis, hepatomegaly	Atelectasis, multiple congenital anomalies, imperforate anus, polycystic kidneys
4 hr., 17 min.	Prematurity	Prematurity, atelectasis, brain injury	
6 hr., 58 min.	Spina bifida, hydrocephalus	Spina bifida, cerebral hemorrhage	
7 hr., 2 min.	Cerebral injury	Cerebral injury	Atelectasis, asphyxia
12 hr.	Cerebral injury	Prematurity, cerebral injury	Prematurity
22 hr.	Prematurity, cerebral hemorrhage	Prematurity, cerebral hemorrhage	Prematurity
26 hr.	Hydrocephalus	Respiratory failure, hydrocephalus	External hydrocephalus, hypoplasia of aqueduct of Sylvius
31 hr.	Cerebral anoxia	Cerebral anoxia	Cerebral anoxia
4 days	Erythroblastosis fetalis	Erythroblastosis fetalis; cerebral hemorrhage?	Erythroblastosis fetalis

Seven infants were stillborn, of whom five were anencephalic. Four of these anencephalic babies were undoubtedly premature (weights 940 to 1,360 gm.). The fifth infant weighed 1,610 gm., but the gestation period was said to be 38 weeks. The sixth stillborn infant had spina bifida and meningocele. The seventh was one of twins delivered by breech extraction, and necropsy showed no obvious reason for death, such as hemorrhage, meningeal tear or fracture.

Twenty-eight of the 57 infants died before the age of 9 months. Six of those dying in the first week had demonstrable intracranial damage. Five of the six were delivered spontaneously without any difficulty, and the sixth was born by breech extraction, hydramnios being present, but the delivery was not considered difficult. The mother, however, had diabetes mellitus and the gestation period was 36 weeks. All six had gross intracranial hemorrhage. Two of the six had lacerations of the falx, one had intraventricular

hemorrhage and three had gross subarachnoid hemorrhage. The baby delivered by breech extraction lived five days and at necropsy was found to have subarachnoid and subpial hemorrhages. It would seem that the so-called difficulties of delivery had little to do with the occurrence of intracranial hemorrhage in this group, although the lesions which were demonstrated were definitely traumatic in origin.

Twelve other infants died during the first week of life. Postmortem examination was carried out in 10 instances (table 1). Also 10 additional babies lived for periods ranging from 18 days to eight months (table 2). All 22 babies in these two groups had gross lesions. In 20 of them the clinical and pathologic findings were such as to preclude injury at birth or difficulties during delivery as causes of death. The other two babies quite probably suffered from birth injury. One baby had a subdural hydroma which was evacuated surgically but the child survived for only 10 weeks. His was a "difficult delivery" and this undoubtedly contributed to, or was responsible for, his death. At the onset of the second stage of labor, the fetal heart sounds could not be heard and manual rotation of the head followed by forceps extraction was carried out. When the child was 19 days old, retinal hemorrhages and a congenital anomaly of the retina were found by the ophthalmologist. Craniotomy disclosed a left temporal hydroma that contained clear yellow fluid, and the brain appeared small and shrunken. The infant remained apathetic, jaundiced and vomited frequently. He died at the age of 10 weeks elsewhere and no postmortem examination was made. It seems most likely that this child had cerebral

TABLE 2

DATA ON 10 BABIES WHO LIVED 18 DAYS TO 8 MO.

Lived, days	Diagnosis	Clinical Cause of Death	Diagnosis at Necropsy
18	Anencephaly	Anencephaly	
26	Meningomyelocele	Meningitis	Meningitis
30	Mongolism, congenital heart disease	Congenital heart disease	Congenital heart disease
32	Meningocele	Respiratory failure	
47	Meningo-encephalocele	Asphyxia	
61	Meningomyelocele	Meningitis	Meningitis
70	Subdural hematoma	Presumably brain injury or abnormality	
148	Intraventricular hemorrhage with hydrocephalus (blood in ventricular tap)	Otitis media, hydrocephalus	Hydrocephalus, otitis media
150	Mongolism	Pneumonia	
240	Lumbar meningomyelocele with paralysis	Meningitis	

damage with a subdural hematoma from manipulation, although the congenital retinal anomaly and the shrunken brain suggested that other anomalies might have been present.

The second injured baby was noted at birth to have a bulging anterior fontanel. At 1 month of age ventricular tap showed grossly bloody fluid. At 12 weeks the presence of communicating hydrocephalus was demonstrated by means of dye injection, and choroiditis and pallor of the optic disks were noted. The child died at 16 weeks of age. Necropsy showed otitis media and communicating hydrocephalus. It is possible that this baby was injured at birth and had intraventricular hemorrhage and resultant hydrocephalus. If this were the case, one would expect the hydrocephalus to be of the obstructive type. However, the hydrocephalus was proved by dye injection and at necropsy to be communicating in type: therefore, the ventricular hemorrhage may have been only coincidental, that is, it was the result of trauma but not the cause of the hydrocephalus.

Twenty-two of the 57 babies remained alive for more than eight months. Two of these were microcephalic and were placed in institutions. Six had mongolism. Whether the latter condition is primarily neurologic is perhaps debatable, but there is no question that the central nervous system is grossly abnormal. All six infants were placed in institutions immediately on leaving the hospital. Five babies had multiple structural abnormalities of the central nervous system, for example, spina bifida, myelomeningocele, hydrocephalus and myelodysplasia. Little could be expected in the way of improvement in these cases, as the lesions were gross.

There remained nine babies who lived more than eight months and on whom follow-up studies could give useful information. Three of these babies were born by spontaneous delivery without difficulty.

One of the three babies born by spontaneous delivery was premature, weighing 1,280 gm., and had generalized convulsive twitchings with cyanosis which began on the eleventh day when the value for blood calcium was 7.46 mg./100 cc. of serum. After suitable treatment the value for blood calcium rose to 10.4 mg. The child appeared to be well at the time of dismissal from the hospital. At the age of 17 months, she was well and had not had any more convulsions, but she did have bilateral internal strabismus. The second infant was a normal-appearing baby who weighed 3,930 gm., and had a small scleral hemorrhage. On the seventh day he had one generalized convulsion. He had no further trouble and was quite well at 4½ years of age. The third child had twitching and clonic movements during the neonatal period, but was well at 7 months. It has not been possible to follow his course until the present.

Of the 9 babies, one delivered by cesarean section had multiple congenital abnormalities. He was premature, weighed 1,250 gm., had harelip, cleft palate, retrolental fibroplasia, and subsequently, at the age of 20 months, convulsive attacks. This child is still under observation.

Three of the nine babies were delivered with outlet forceps. The first was subjected to a labor of 33 hr. One week later he had twitching of the extremities and the value for his blood calcium was 8.6 mg./100 cc. Following suitable therapy he had remained quite well to the age of 18 months. The second baby, on the ninth day, had twitching of the left side of the face and left arm, which was followed by a generalized convulsion. He was apparently well on dismissal from the hospital and has remained well up to 2 years of age. The third infant had some cyanosis and twitching of muscles on the day following delivery but was well at the time of dismissal from the hospital. It has not been possible to trace this infant.

Two of these nine infants were born after difficult deliveries. The first was born by breech extraction and exhibited bilateral brachial palsy. The delivery in this case was described as a "difficult, grade 3" breech extraction at term. Asphyxia was present and respiration was delayed for 12 minutes. The only evidence of injury, however, was the brachial palsy due to trauma of the upper branches of the brachial plexus. No special treatment was carried out and the paralysis disappeared completely in two months. The child was quite well a year later. The delivery in the second case was accomplished by low forceps extraction which was difficult owing to a contracted pelvis. The baby had two convulsive seizures a few hours after delivery but had no other difficulties and was well at 15 months of age.

Comment

Among the 57 babies with neurologic lesions, only five had been subjected to unusual manipulation during birth. One of these, who died 26 hours after delivery, had hydrocephalus which was probably the cause of the dystocia rather than the result. Another died 31 hours after birth by difficult breech delivery. At birth this baby was pallid and apneic and exhibited attacks of cyanosis. The baby may well have died as the result of difficulty in delivery but postmortem examination revealed no sign of gross or microscopic hemorrhage or damage to the central nervous system. One baby suffered from a subdural hydroma, in all probability the result of birth injury, and survived for only 10 weeks. Two infants had birth injuries but recovered and had no clinical evidence of residual lesions after 15 months and one year respectively.

Summary

Among 4,464 births which took place during a period of four years, 1944 through 1947, there were 57 infants who had demonstrable neurologic lesions. Six of the 57 died with conclusive evidence of gross intracranial hemorrhage due to trauma. None of the six had been subjected to "difficulties of labor," five having had spontaneous births and one having been born by breech delivery which was not considered difficult.

Twenty-two other infants died within a few minutes after birth or after intervals of days or weeks. Twenty of these had gross lesions of such type that injury at birth or difficulties during delivery definitely could not be considered the cause of death. The other two probably had injuries due to difficulties of birth but one had hydrocephalus which may have been the cause and not the result of the injury.

Of the remaining 22 infants who survived for nine months or more, 13 had gross neurologic abnormalities. Two of the remaining nine were subjected to difficulty during birth. One had bilateral brachial palsy and one had two convulsive seizures. Both were quite normal at 1 year and at 15 months of age, respectively. Six of the nine had muscle twitchings or convulsions, but were well after intervals of seven months to 4½ years. These children must be observed for many years to determine what their future course may be. The remaining child had multiple congenital abnormalities and experienced convulsions.

Among the 57 infants, there were only five who had frankly difficult births. Two recovered completely. One died with a subdural hematoma, one with hydrocephalus and intraventricular hemorrhage, and one after attacks of cyanosis. Delivery in the last case was a "difficult breech," but necropsy showed evidence of anoxia with no hemorrhage.

It seems reasonable to conclude that difficulties during delivery had comparatively little to do with persistent neurologic abnormalities in most of the infants who survived.

II. Role of Prolonged Labor, Asphyxia and Delayed Respiration

In order to study the influence of various factors that may operate to produce trauma in infants during birth, a careful survey has been made of the condition of babies born in the period January 1, 1944, through June 30, 1946, in St. Mary's Hospital, Rochester, Minn. The total number of babies born in this period was 2,306 to 2,281 mothers. Accurate notes were made on various aspects of the mother's labor in each case and records were kept on the findings of physical examination of the babies when newborn and in well-baby clinics. The purpose of the study is to determine what influence the evident difficulties of labor may have on a child's subsequent physical and mental progress, to note particularly neurologic abnormalities, and to investigate the occurrence of such conditions as subdural hematoma, cerebral palsy and convulsions. This will necessitate observations over an extended period. In this preliminary study the condition of most of these infants has been followed for one to four years. During this interval gross abnormalities as a result of birth injuries should be evident. Convulsive disorder, of course, may appear at a later date. Sixty and four-tenths per cent of the babies have been observed in well-baby clinics for one to four years, and reports from physicians and parents have been obtained on 20.2%. The condition of the remaining 19.4% has not been followed for at least one year. It is true that there may be some children with minor difficulties, but certainly obvious neurologic conditions would be observed and reported.

The grouping of the cases according to certain factors which involved labor and delivery and which formed the basis for selection of cases for this study was as follows:

Group 1: Prolonged first stage of labor (more than 1,000 minutes). Prolonged second stage of labor (primipara, more than 120 minutes; multipara, more than 60 minutes). Both first and second stages prolonged.

Group 2: Controls for group 1.

Group 3: Asphyxia livida or pallida. Delayed respiration (beyond 1 minute).

Group 4: Controls for group 3.

Role of Length of Labor

Group 1. Prolonged Labor.—Of the 2,281 mothers, 213 had prolonged labor. These 213 mothers gave birth to 216 infants. During the neonatal period 197 (91.2%) of these infants were considered normal, and 19 (8.8%) were abnormal. Seven of these abnormal babies were stillborn or died, and death could be ascribed to birth injury in 3 of them. Of the remaining 12 abnormal infants, 7 had cyanotic spells, 3 twitching of muscles, 1 temporary paralysis of the lip, and 1 laceration of an eyelid during the neonatal period.

Group 2. Controls for Group 1.—From the total group of 2,281 mothers, 213 who had relatively short uncomplicated labor were arbitrarily chosen as controls. To these 213 mothers, 213 infants were born. Two hundred and five (96.2%) of these infants were considered normal, and 8 (3.8%) were abnormal. In this group, 4 were stillborn or died but only 1 death could be ascribed to injury, intracranial hemorrhage being present (table 3). Of the remaining 4 abnormal infants, 1 had cyanotic attacks, 1 muscle twitch-

TABLE 3

FATE OF INFANTS AFTER PROLONGED OR NORMAL LABOR: NEONATAL PERIOD

	Prolonged Labor		Normal Labor	
	No.	Per Cent	No.	Per Cent
Normal infants	197	91.2	205	96.2
Abnormal infants	19	8.8	8	3.8
Stillbirths	3	1.4	2	0.9
Died	4*	1.9	2†	0.9
Cyanotic attacks	7	3.2	1	0.5
Muscle twitching	3	1.4	1	0.5
Paralysis, lip	1	0.5	1	0.5
Laceration, eyelid	1	0.5	—	—
Temperature to 38.8°C.	—	—	1	0.5
Totals	216	100.0	213	100.0

* Three died as a result of trauma.

† One died as a result of trauma.

ing, 1 paralysis of the lip and 1 elevation of temperature to 38.8° C. during the neonatal period.

From the foregoing observations it would appear that prolonged labor increases the risk of cerebral injury and death during the neonatal period.

Follow-up Studies of Group 1.—Twelve of the 19 abnormal infants in this group survived the neonatal period. Eleven of these 12 children were followed to the ages ranging from 1 to 4 years and all were normal (one not traced).

Nine of the 197 presumably normal children in this group had neurologic signs or symptoms after the neonatal period. One had ptosis of an eyelid which disappeared before the age of 7 months. One had a convulsion (nonfebrile) at the age of 17 months. Four had febrile convulsions at 15 months, 25 months, 32 months and 21 months, respectively, but appeared normal at a later date. One had strabismus, observed at 3 years of age. One had an attack of "disorientation" at 25 months, and one had torticollis at 5 months of age but was normal at 4 years. If we include the child with "disorientation," 6 of the 21 abnormal children in group 1 (28.6%) had convulsions of some type.

Follow-up Studies of Group 2 (Controls).—Four of the 8 abnormal infants in this group survived the neonatal period; 1 had cyanotic attacks, 1 muscle twitching, 1 paralysis of the lip and 1 elevation of temperature to 38.8° C. in the neonatal period. Three of these 4 children were normal and healthy at 3 to 4 years of age (1 not traced). Ten other infants had neurologic symptoms or signs at a later date. Four of the 10 had febrile convulsions at ages ranging from 1 year to 4 years. Three had strabismus at 4 years of age. Three had convulsive disorders before the age of 4 years, and 1 of these died in a convulsion at 26 months of age. Of the 14 "abnormal" infants in this group, 7 (50%) had convulsions of some type (tables 3 and 4).

If the infants who had "prolonged" deliveries (group 1) are compared with those who had "normal" deliveries (group 2), it is evident that there is little, if any, difference in their subsequent development. We may then conclude that prolonged delivery, if the infant survives, did not cause increased incidence of neurologic disturbances. In fact, during the first four years of life, more children had convulsive disorder in the "normal" or control group than in the group in which prolonged labor occurred.

TABLE 4

FATE OF INFANTS AFTER PROLONGED OR NORMAL LABOR: 1 TO 4 YR. AFTER BIRTH

	Prolonged Labor		Normal Labor	
	No.	Per Cent	No.	Per Cent
Normal infants	170	95.0	154	93.9
Abnormal infants	9	5.0	10	6.1
Febrile convulsions	4	2.2	4	2.4
Strabismus	1	0.6	3	1.8
Convulsive disorder	2	1.1	3	1.8
Ptosis, eyelid	1	0.6	—	—
Torticollis	1	0.6	—	—
Totals	179*	100.0	164†	100.0

* Of the 209 infants living at the end of the neonatal period (total of 216 less 7 who died), 1 infant died before the end of the 1st yr. and 29 infants have not been followed-up for at least 1 yr.

† Of the 209 infants living at the end of the neonatal period (total of 213 less 4 who died), 2 infants died before the end of the 1st yr. and 43 infants have not been followed-up for at least 1 yr.

ROLE OF ASPHYXIA AND DELAYED RESPIRATION

Group 3. Asphyxia and Delayed Respiration Present.—There were 111 babies in this category, and 84 (75.7%) of these were normal and 27 (24.3%) were abnormal in the neonatal period. Fourteen of the 27 abnormal babies (12.6% of 111 babies) died in the neonatal period, 10 of them being premature and 5 of the premature babies weighing 1,000 gm. or less; the other 4 deaths were ascribed to intra-uterine asphyxia, multiple congenital anomalies, cerebral anoxia and cerebral hemorrhage, respectively. It is interesting that this last baby, the only one with demonstrable cerebral injury, was a second child, and was delivered spontaneously after 245 minutes of normal labor (table 5).

Of the remaining 13 infants who had evidence of abnormality at birth, one had mongolism and was admitted to an institution and died there some months later. Another had

TABLE 5

FATE OF INFANTS HAVING ASPHYXIA OR DELAYED RESPIRATION, WITH CONTROLS: NEONATAL PERIOD

	Asphyxia or Delayed Respiration		No Asphyxia	
	No.	Per Cent	No.	Per Cent
Normal infants	84	75.7	108	97.3
Abnormal infants	27	24.3	3	2.7
Died	14		2	
Cyanotic attacks	6			
Apnea	1			
Asphyxia pallida	1			
Mongolism	1		1	
Subdural hydroma*	1			
Muscle twitching	2			
Weakness, poor cry	1			
Totals	111	100.0	111	100.0

* Died at the age of 10 wk.

subdural hydroma drained surgically, but died at 10 weeks of age. Two who were babies of diabetic mothers had cyanosis and twitching muscles, respectively; 1 of these infants was normal four years later, but the other infant could not be traced. Six other infants had attacks of cyanosis only, neonatally, but all 6 without exception appeared to be normal children when examined at 2 or 3 years of age. One other had apnea and was revived with oxygen. He appeared normal at 4 years of age. Still another had asphyxia pallida but appeared normal at 2½ years with an intelligence quotient of 121. The last infant in this group was weak and had a very poor cry at birth but appeared normal at 1 year of age.

Group 4. Controls for Group 3.—A group of 111 babies who did not have asphyxia or delayed respiration was arbitrarily chosen as controls for the group of babies who did have these conditions. One hundred and eight (97.3%) of those infants were normal in the neonatal period, 2 (1.8%) died, and 1 had mongolism. Of the 2 who died, 1 had patent ductus arteriosus and 1 cerebral hemorrhage.

TABLE 6

FATE OF INFANTS HAVING ASPHYXIA OR DELAYED RESPIRATION, WITH CONTROLS: 1 TO 4 YR. AFTER BIRTH

	Asphyxia or Delayed Respiration		No Asphyxia	
	No.	Per Cent	No.	Per Cent
Normal infants	82	95.3	84	95.4
Abnormal infants	4	4.7	4	4.6
Mongolism	1			
Strabismus	1		1	
Convulsions	1		3	
Torticollis	1			
Totals	86	100.0	88	100.0

Follow-up Studies of Group 3 (Asphyxia).—Follow-up studies could be made on 86 of these patients for one year or more. Of these, 4 had abnormalities. In the first of these 4 babies a diagnosis of mongolism was made sometime after birth. In the second, strabismus developed by the age of 2½ years; this child's intelligence quotient was 130. The third child was reported to have had a doubtful convulsive episode at 7 months of age. In the fourth, torticollis developed in infancy but disappeared before 4 years of age. The remaining 82 children appeared normal.

Follow-up Studies of Group 4 (Controls).—It was possible to follow-up 88 of these infants for at least one year. Eighty-four appeared normal. Of the 4 in whom abnormalities developed, 1 had strabismus, 2 had febrile convulsions, and 1 had febrile convulsions followed by petit mal attacks.

It is interesting to note that of all those infants who were asphyctic and who survived, in only 1 did convulsions develop by 4 years of age, and it was even doubtful that this occurred. On the other hand, of an equal number of babies who did not have asphyxia, febrile convulsions developed in 3 before 4 years of age and 1 of these continued to have petit mal attacks. It would certainly seem, then, that neonatal asphyxia with cyanotic attacks did not necessarily predispose to convulsive attacks (tables 5 and 6).

TABLE 7

PREMATURE BABIES WITH AND WITHOUT ASPHYXIA OR DELAYED RESPIRATION AT BIRTH: WT. LESS THAN 2,500 GM.

Respiratory Delay, Min.	Lived	Died	Total
1–5	3	0	3
6–10	1	2	3
11–15			
More than 15		1	1
None	6	5	11
Not stated	1	2	3
Totals	11	10	21

It was of interest to the authors to study particularly the premature babies who had asphyxia or delayed respiration (table 7). All infants whose weights were less than 2,500 gm. were considered premature. There were 21 such babies. Ten of them were normal in the neonatal period, and 9 of these 10 were found to be normal after 1 year of age, while in 1 strabismus developed. One other baby had a series of cyanotic spells, but was a normal child at 2 years of age. As previously noted, 10 infants died, 5 of them weighing 1,000 gm. or less, 4 weighing less than 2,000 but more than 1,000 gm. and 1 weighing 2,390 gm. and having asphyxia pallida. None of these infants had intracranial hemorrhage at necropsy.

Three premature infants had a delay in the onset of respiration of 1 to 5 minutes and survived. Three others had a delay of 6 to 10 minutes, and 2 of these died. One whose respiration was delayed more than 15 minutes died. On the other hand, 11 premature infants had no delay in onset of respiration, and of these, 5 died. In 3 others, no note was made of the length of delay in respiration and 2 of these died. It was possible to

TABLE 8

INFANTS WHO HAD ASPHYXIA OR DELAYED RESPIRATION: WT. MORE THAN 2,500 GM.

Respiratory Delay, Min.	Neonatal Period				Follow-up Period (1–4 yr.)			
	Total No.	Normal	Died	Abnormal	Total No.	Normal	Abnormal	No Follow-up
Not stated	16	12	2	2	14	13	1	0
1–5	30	25	0	4	30	24	1	5
6–10	16	14	0	2	16	15	0	1*
11–15	6	6	0	0	6	5	0	1
More than 15	4	2	2	0	2	2	0	0
Totals	72				68			

* Died before the end of the 1st yr.

follow-up all 11 babies who survived. Ten developed normally, and 1 had strabismus but appeared quite normal otherwise, with an intelligence quotient of 130.

Seventy-two infants of the group which had asphyxia had delayed onset of respiration but were not considered premature (table 8). Thirty of these full term infants had a delay of 1 to 5 minutes in the onset of respiration. Twenty-six of the 30 appeared normal in the neonatal period, and 4 had cyanotic attacks. After 1 to 4 years of age, 24 appeared normal, 1 was said to have an "attack" which might be considered a convulsion, and 5 were not traced.

Sixteen of the 72 infants had a delay of 6 to 10 minutes in the onset of respiration. Fourteen of the 16 appeared normal in the neonatal period, 1 had mongolism, and 1 had asphyxia pallida. Fifteen remained normal after 1 year of age. The child with mongolism died before the end of the first year.

Six of the 72 infants had a delay of 11 to 15 minutes in the onset of respiration. All 6 appeared normal in the neonatal period, and 5 still appeared normal after one year. One was not traced.

Four infants had a delay in onset of respiration of more than 15 minutes. Two of these 4 appeared normal during the neonatal period and still appeared normal after 1 year of age. Two died, 1 of multiple congenital anomalies and 1 of cerebral anoxia.

Sixteen infants had delay in respiration but the number of minutes was not stated. Twelve of the 16 appeared normal neonatally. Two died, 1 of intra-uterine asphyxia and the other of intracerebral hemorrhage. Another had a rather weak cry, but appeared normal in one year. The remaining infant had cleft palate and cyanotic attacks but appeared normal at 4 years of age. In follow-up studies, 13 of the 14 living children appeared normal at 1 to 4 years of age, and the other had a diagnosis of mongolism which had not been made in the neonatal period.

Comment

From these observations it would appear that both premature and full term infants who had asphyxia or delayed respirations either died or recovered completely and developed normally (table 8).

Hunt and Foust[26] have compiled data which tend to confirm these findings. They studied 86 extremely difficult deliveries among 12,500 occurring in the Section on Obstetrics and Gynecology of the Mayo Clinic. There were 8 stillbirths and 4 neonatal deaths in the 86 deliveries; the corrected infant mortality rate was 8.1%. They were able to follow-up 43 children during intervals ranging from six weeks to 26 years. Twenty-two of these children had been followed-up for less than six years. In this latter group appeared 1 impaired child who suffered from convulsive disorder. Fifteen of the 43 children were followed-up for 10 to 26 years and were apparently normal with the exception of 1 who died from an entirely irrelevant cause. One other had partial inability to rotate externally the right lower extremity.

A number of interesting facts emerged as a result of the present study:

1. Two hundred thirteen of 2,281 mothers had prolonged labor, an incidence of 9.3%.

2. There were 111 asphyxiated infants among 2,306 newborn infants, an incidence of 4.8%.

3. The average age of mothers having prolonged labor was 25.8 years or 2.0 ($\pm$ 0.5) years younger than those with normal labor (27.8 years).

4. Seventy per cent of those mothers having prolonged labor were primiparous, whereas 32.4% of those having normal labor were primiparous. The infants born following prolonged labor were 74 gm. (2½ ounces) heavier on the average, than those infants whose mothers had normal labor.

5. Among those babies subjected to prolonged labor 54.6% were males and 45.3% were females, but among those subjected to normal labor, 50.2% were males and 49.8% females.

6. The type of delivery varied considerably in the two groups. There were 26.4% spontaneous deliveries, 5.6% breech deliveries, 67.6% forceps deliveries and 0.4% cesarean deliveries in the group in which delivery was prolonged, while there were 79.8% spontaneous, 3.3% breech, 12.2% forceps and 4.7% cesarean deliveries in the group in which delivery was not prolonged.

7. The incidence of retention of the placenta, premature separation of the placenta and looping of the cord about the baby's neck was essentially the same among those with prolonged labor and those with normal labor.

8. The color of the newborn infant was affected by the type of labor. There were 8.4% more babies with normal color than with abnormal color in the group in which labor was normal, while there were 7% more with asphyxia pallida and livida than with normal color in the group in which labor was prolonged.

9. In the asphyxiated group of infants, 57.6% were not delivered spontaneously while in the control group only 24.4% were not delivered spontaneously.

10. There were 8 asphyxiated babies who had prolapse of the cord or knots in the cord. There were none with these conditions in the control group.

11. Of the asphyxiated infants, 6 (5.4%) were associated with placenta previa and 6 (5.4%) with retained placenta. In the control group, 3 (2.7%) were associated with placental previa and none with retained placenta.

12. Of asphyxiated infants, 56 (54.5%) mothers were primiparous. In the control group, 33 (29.7%) were primiparous.

13. Among the asphyxiated infants, there were more premature and more large infants than among the controls.

Summary

A survey was made to determine the relationship of prolonged labor, asphyxia and delayed respiration to the occurrence of trauma and, thereby, neurologic lesions of the infant. As might be expected, prolonged labor appeared to increase the risk of intracranial injury and death of the infant. However, if the infants survived, there was little or no abnormality in subsequent development and no increase in neurologic disturbances, at least during the first few years of life. More children had convulsive disorder in the "normal" or control group than in the group of those subjected to prolonged delivery. The same held true among the infants who were asphyxiated, that is, there were more who had convulsive disorder in the control group than among those who were asphyxiated. There were more deaths and more abnormal infants among those who were asphyxiated, but these included a considerable number of premature infants, many of them being not viable. If the infants survived the neonatal period, they developed normally, or at least no more abnormalities were noted among those who were asphyxiated than among the controls.

Anoxia caused by delay in respiration did not have a serious prognosis in those infants who survived the neonatal period. Even a delay of 11 to 15 minutes, while fatal

in 2 instances, did not appear to cause any abnormality, at least during the first four years of life, in the infants who survived.

References

1. Little, W. J., On influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on mental and physical condition of child, especially in relation to deformities, Tr. Obst. Soc., London **3**:293, 1862.
2. McNutt, Sarah J., Apoplexia neonatorum, Am. J. Obst. **18**:73, 1885.
3. Freud, S., Die infantile Cerebrallähmung, Vienna, A. Holder, 1897.
4. Collier, J., Cerebral diplegia, Brain **22**:373, 1899.
5. Collier, J., Pathogenesis of cerebral diplegia, Brain **47**:1, 1924.
6. Weyhe, E., Ueber die Häufigkeit von Hämorrhagien in Schädel und Schädelinhalt bei Säuglingen, Kiel, A. F. Jensen, 1889.
7. Ylppö, A., Einige Kapitel aus der Pathologie der frühgeborenen Kinder, Klin. Wchnschr. **1**:1241, 1922.
8. Beneke, Ueber Tentoriumzerreissungen bei der Geburt, sowie die Bedeutung der Duraspannung für chronische Gehirnerkrankungen, München. med. Wchnschr. **57**(pt. 2):2125, 1910.
9. Seitz, L., Ueber Hirndrucksymptome bei Neugeborenen in Folge intracranieller Blutungen und mechanischer Hirninsulte, Arch. f. Gynäk. **82**:528, 1907.
10. Ehrenfest, H., Birth Injuries of Child, New York, D. Appleton & Company, 1922.
11. Ford, F. R., Diseases of Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944.
12. Craig, W. S., Intracranial haemorrhage in newborn: Study of diagnosis and differential diagnosis based upon pathological and clinical findings in 126 cases, Arch. Dis. Childhood **13**:89, 1938.
13. McGuinness, F. G., Significance of intra cranial injury of newborn with accompanying haemorrhage, Canad. M. A. J. **48**:206, 1943.
14. MacGregor, A. R., Pathology of still-birth and neonatal death: Review of 1053 cases, Brit. M. J. **4**:174, 1946.
15. Campbell, Kate, Intracranial disorders of new born associated with birth, M. J. Australia **2**:57, 1948.
16. Hannes, W., Zur Frage der Beziehungen zwischen asphyktischer und schwerer Geburt und nachhaltigen psychischen und nervösen Störungen, Ztschr. f. Geburtsch. u. Gynäk. **68**:689, 1911.
17. Fazekas, J. F., Alexander, F. A. D., and Himwich, H. E., Tolerance of newborn to anoxia, Am. J. Physiol. **134**:281, 1941.
18. Smith, C. A., Physiology of Newborn Infant, Springfield, Ill., Charles C Thomas, Publisher, 1945.
19. McPhail, F. L., and Hall, E. L., Consideration of cause and possible late effect of anoxia in newborn infant, Am. J. Obst. & Gynec. **42**:686, 1941.
20. Schreiber, F., Neurologic sequelae of paranatal asphyxia, J. Pediat. **16**:297, 1940.
21. Lund, C. J., Prevention of asphyxia neonatorum: Study of etiologic factors observed in 2,000 consecutive deliveries, Am. J. Obst. & Gynec. **41**:934, 1941.
22. Courville, C. B., and Marsh, C., Neonatal asphyxia: Its encephalic residuals and mechanism of their production, Bull. Los Angeles Neurol. Soc. **9**:121, 1944.
23. Clifford, S. H., Effects of asphyxia on newborn infant, J. Pediat. **18**:567, 1941.
24. Darke, R. A., Late effects of severe asphyxia neonatorum: Preliminary report, J. Pediat. **24**:148, 1944.
25. Windle, W. F., Structural and functional alterations in brain following neonatal asphyxia, Psychosom. Med. **6**:155, 1944.
26. Hunt, A. B., and Foust, G. T., Jr., Difficult labor in relation to forceps delivery, New Orleans M. & S. J. **102**:239, 1949.

Spanish Abstract

Lesiones Neurologicas en el Recién Nacido. Efectos del Parto Prolongado, de la Asfixia y de la Respiracion Retardada

Se reporta el resultado de un estudio sobre las condiciones fisicas de 578 recién nacidos con el proposito de determinar las influencias del parto prolongado, de la asfixia, y de la respiracion

retardada en la produccion de traumas y lesiones neurologicas en los recién nacidos. Como es de sospecharse el parto prolongado aumenta considerablemente el riesgo de injuria intracranial y muerte del recién nacido. En los niños que sobrevivieron el parto prolongado no se encontraron abnormalidades en el desarrollo ulterior de los niños, asi como tampoco se encontró aumento de las alteraciones neurologicas durantes los primeros años de la vida. Mas niños sufrieron de convulsiones en el grupo normal de control que en el group de casos que sufrieron de parto prolongado. Resultados semejantes se obtuvieron en los niños asfixiados en los cuales la incidencia de convulsiones fué menor que en el grupo de control. Sin embargo la mortalidad fué mayor en el grupo de asfixiados, pero debe tenerse en cuenta que en este grupo se incluyó un gran numero de niños prematuros, muchos de los cuales eran no-viables. En el grupo de niños asfixiados qué sobrevivieron el periodo neonatal todos se desarollaron normalmente o al menos las abnormalidades notadas no fueron mayores en el grupo de asfixiados que en el grupo de controles normales. En los casos de anoxia causada por respiracion demorada que sobrevivieron el periodo neo-natal, el prognostico fué bueno. Aún en los casos con una demora de la respiracion de 11 a 15 minudos no se notaron abnormalidades neurologicas durantes los primeros cuatro años de la vida en los niños que sobrevivieron. En este ultimo grupo hubo dos fatalidades.

Mayo Clinic

TREATMENT OF THYROTOXICOSIS IN CHILDREN WITH THIOUREA DERIVATIVES

By RALPH H. KUNSTADTER, M.D., AND ALBERT F. STEIN, M.D.
Chicago

INTRODUCTION

THE most satisfactory management of thyrotoxicosis in children is unsettled. There are those who recommend surgery in almost all cases [1-4] and others who advocate only medical management.[1]

Those who favor surgery argue that permanent cure is attained by this method only.[2-4] Furthermore, prolonged medical treatment may result in psychic disturbances because of prolonged restrictions, and may militate against normal growth and development by permitting a prolonged state of subacute hyperthyroidism to exist. Also, prolonged medical treatment involves excessive medical costs.[1]

Those who advocate medical management argue that operative mortality, although low, is ever present. In a recent discussion on the treatment of exophthalmic goiter in children, Topper[1] states that postoperative complications and sequelae are frequent in childhood, viz.: postoperative toxicity, tetany, recurrent laryngeal paralysis, keloid scar formation and hypothyroidism. Postoperative recurrences and persistence of hyperthyroidism are fairly frequent, particularly in children.[1]

In 109 children thyroidectomized for exophthalmic goiter at the Mayo Clinic from 1921 to 1945 there were three deaths. Follow-up data on 102 cases showed seven recurrences and 23 instances of hypothyroidism. In the same period 14 cases were treated medically. Results were good in 10 cases, fair in three and poor in one.[5]

In a report based on observations of 62 patients over a 25 year period, Reilly[6] found that results were successful in 15 of 30 patients treated conservatively. The other 15 failed to respond and either surgery or roentgen ray therapy was used. In those operated upon, there were recurrences in 6%, permanent hypothyroidism in 3 patients and permanent hypoparathyroidism in 2 patients.

Of 23 children with hyperthyroidism treated by McIntosh,[7] 19 were subjected to subtotal thyroidectomies and 4 were treated without surgery. Included in the group of children operated on were 9 complete arrests, 3 nearly complete arrests, 5 recurrences and 2 deaths. Based upon a review of previous reports on the treatment of childhood thyrotoxicosis and his own experience, McIntosh[7] points out that "children deserve an adequate trial of medical management before surgery is advised and that in a considerable number of them surgery is neither necessary nor advisable." This opinion is shared by Topper[1] in a recent report of a follow-up study in 12 cases of exophthalmic goiter in children and by Williams and Janney,[8] who, in 1947, were the first to report on the treatment of thyrotoxicosis in children with thiouracil.

From the Children's Endocrine Clinic, and the Sarah Morris Hospital for Children, Chicago.

Presented at the Eighteenth Annual Meeting of the American Academy of Pediatrics, San Francisco, Nov. 16, 1949.

(Received for publication Oct. 24, 1949.)

Because the present investigators share the opinions of Reilly,[6] McIntosh,[7] Topper[1] and Williams and Janney[8] that conservative management is desirable before surgery is advocated, the following report on experience with thiourea derivatives in the treatment of thyrotoxicosis in children is presented.

Clinical Material

During the past 6 yr. the authors have treated 9 cases of moderate to severe primary hyperthyroidism in children with thiourea derivatives; the 1st 2 cases with thiouracil, the 3rd with thiouracil, propylthiouracil and methylthiouracil, respectively, and subsequently 1 with methylthiouracil and 5 with propylthiouracil. Thiouracil has been discarded in favor of propyl and methylthiouracil which are less toxic. Methylthiouracil has no advantages over propylthiouracil which was used in the majority of cases.

There were 6 females and 3 males in this group, their ages varying from 5 to 15 yr. Two of the children, both females, were Negroes and 1 child, a female, was Mexican.

All patients were hospitalized at the time treatment was initiated. They were ambulant and received sedation for sleep only when deemed necessary. They remained in the hospital until clinical improvement became manifest and/or the basal metabolic rate began to fall. They usually remained no longer than 2 to 3 wk.

All had symptoms of thyrotoxicosis for periods of several weeks to several months. In all instances, the thyroid was moderately to markedly enlarged and of the diffuse type. All had mild to moderate exophthalmos. The average of the initial basal metabolic rates varied from plus 32 to 51.9 with 7 of the 9 cases having rates of over 40. Based upon the severity of the symptoms, size of the thyroid and degree of exophthalmos, 6 were classified severe and 3 moderately severe. (Table 1.)

The drugs were administered in doses of from 150 to 300 mg. or more daily, the smaller doses for the younger and smaller children or those whose disease was not considered severe.

The majority received the accepted adult dose of 200 to 300 mg. or more daily.[3, 4, 9] The daily dose was divided into 3 equal parts and administered at 8 hr. intervals when possible. After a normal basal metabolic rate was established, the dose was gradually reduced and a maintenance dose of 50 to 100 mg. daily was prescribed. While the therapeutic dose was being reduced, basal metabolic rates were taken at from 1 to 2 wk. intervals. These were used as a guide in order to avoid relapses resulting from too rapid reduction of the dose which occurred in 2 of the early cases (Cases 2 and 6).

The plan was to treat all patients for a period of from 6 to 12 mo. or longer, as it has been shown that at least this much time is required to produce a remission.[3, 4, 9]

In those cases where the thyroid failed to decrease in size and thyrotoxicosis was controlled for several months, U.S.P. dessicated thyroid gland .015 to .03 gm. daily was prescribed. It was given either while the patient was receiving maintenance therapy or during the period of remission.

TABLE 1

Cases Treated with Thiourea Derivatives

No.	Name	Age	Sex	Race	Duration of Symptoms	Goiter*	Exophthalmos†	Severity of Disease
1	C.D.	9 yr.	F	W	3½ mo.	xxx	xx	Severe
2	M.K.	12 yr.	M	W	2 mo.	xxx	x	Severe
3	R.F.	13 yr.	F	NW	7 wk.	xxx	xx	Severe
4	D.M.	15 yr.	F	W	4 mo.	xxx	x	Severe
5	A.M.	11 yr.	F	NW	5 wk.	xx	x	Moderate
6	N.G.	9 yr.	F	W	5 mo.	xx	x	Moderate
7	C.C.	5 yr.	F	W Mex.	2 mo.	xxx	xx	Severe
8	J.G.	13½ yr.	M	W	4 mo.	xx	xx	Moderate
9	A.L.	10½ yr.	M	W	3 mo.	xxx	xx	Severe

* Graded 1–4 based upon the degree of enlargement.

† Graded 1–4 based upon relative degree of exophthalmos.

Lugol's solution was administered to all patients preoperatively, beginning 2 to 3 wk. before operation, and postoperatively during convalescence.

Complete blood counts were done and the urine was examined frequently for abnormal changes. The patients were observed closely for jaundice indicative of hemolysis or liver damage. Electrocardiograms were taken periodically on those patients who responded poorly to initial treatment and on those who relapsed.

Results

Of the 9 cases summarized herein, 5 responded satisfactorily to thiourea derivatives alone up to the present time. Four failed to respond to drug therapy and subtotal thyroidectomy was performed.

I. Cases Treated with Thiourea Derivatives

Case 1. Classified severe. C. D., a white female, 9 yr. of age, has been in a remission for 4 yr. following 13 mo. of interrupted thiouracil therapy. BMR fell to normal 28 days following initiation of treatment. She received a daily dose of 300 mg. for 19 days, 400 mg. for 9 days, 300 mg. for 8 days, 200 mg. for 9 days and 100 mg. for 70 days. In addition to thiouracil, she received .03 gm. of U.S.P. dessicated thyroid gland daily during the latter 54 days. A relapse occurred, thyroid was discontinued and thiouracil was increased to 300 mg. daily for 8 days, and subsequently 200 mg. for 10 days and then 100 mg. for 9 days. Due to a drug shortage, she received no medication for the following 21 days. A second relapse occurred during this period, and after a further supply of thiouracil was received she was given 300 mg. daily for 82 days and 200 mg. for 73 days. Due to shortage, the drug was discontinued at this time and she received no thiouracil for the following 8 mo. She remained well during this period but subsequently developed a severe acute upper respiratory infection, following which she had her third and final relapse. Thiouracil was restarted and she received 400 mg. daily for 7 days, 200 mg. for 79 days and finally 100 mg. for 30 days.

Three relapses occurred: 1. Due to overdose of thyroid (.03 gm. daily) given during a remission in an attempt to reduce the size of the thyroid; 2. Due to inadequate treatment resulting from a shortage of drug during the War; 3. Apparently due to a severe upper respiratory infection after a remission of 8 mo. without therapy. At the present age of 15 yr., exophthalmos has receded almost completely and the thyroid is normal in size. Growth and sexual development are normal. She has been under observation for a total period of 6 yr. and is the authors' first patient treated with thiouracil.

Case 5. Classified moderately severe. A. M., a Negro female, 11 yr. of age, has been in a remission for 12 mo. following continuous propylthiouracil therapy for 12 mo. BMR fell to normal 10 days after initiation of treatment. Initially she received a daily dose of 150 mg. for 10 days and 100 mg. for 21 days. At the end of this period BMR had begun to rise and the dose was increased to 200 mg. daily. She received this dose for 68 days and then 50 mg. daily for approximately 9 mo. At the present age of 13 yr., she feels perfectly well and goes to school with unrestricted activities. The exophthalmos has receded considerably and the thyroid is only slightly larger than normal. Growth and sexual development are normal. Menstruation began at 13 yr. of age.

Case 6. Classified moderately severe. N. G., a white female, 9 yr. of age, has been in a remission for 14 mo. following continuous propylthiouracil therapy for 7 mo. BMR fell to normal 10 days after initiation of treatment. Initially she received a daily dose of 150 mg. for 4 days, 100 mg. for 7 days and 50 mg. for 20 days. During this latter period she experienced a mild relapse and the dose was increased to 100 mg. daily. She received this dose for 130 days and subsequently 75 mg. for 14 days and finally 50 mg. for 35 days.

The mild relapse that occurred during the first month of treatment apparently was due to too rapid reduction of the dose of the drug. After her basal metabolic rate had reached normal, the daily dose was reduced from 150 to 50 mg. in less than 2 wk. At the present age of 11 yr., she is feeling perfectly well and is going to school with unrestricted activities. The thyroid had decreased considerably in size and there is no longer exophthalmos. Growth is normal.

Case 7. Classified severe. C. C., a white Mexican female, 5 yr. of age, the youngest patient in this series, was treated with propylthiouracil for 15 mo. BMR fell to normal 14 days after initiation of treatment. Initially she received 150 mg. daily for 17 days, 100 mg. for 11 days and 50 mg. for 8 mo. At the end of this period she experienced a severe acute upper respiratory infection followed by a moderately severe relapse. The dose was increased to 200 mg. daily and continued for 3 mo. Subsequently she received 100 mg. daily for 30 days and finally 50 mg. for 60 days. She has been in a remission without therapy for 7 mo. At the present age of 7 yr. she is in good health. Her exophthalmos

has not receded and her thyroid is still considerably enlarged but smaller than at the time treatment was begun. Growth is normal.

Case 8. Classified moderately severe. J. G., a white male, 13½ yr. of age, has been in a remission for 3 yr. without therapy following continuous treatment with propylthiouracil for 6 mo. BMR fell to normal 18 days after initiation of treatment. Initially he received 200 mg. daily for 21 days, followed by 100 mg. for 30 days, 75 mg. for 28 days and finally 50 mg. for 105 days. At the present age of 17 yr., he is perfectly well. There is no exophthalmos and thyroid is normal in size. Growth and sexual development are normal. At the present time, he is engaging in high school varsity football.

II. Cases Treated with Thiourea Derivatives and Followed by Subtotal Thyroidectomy

Case 2. Classified severe. M. K., a white male 12 yr. of age, was treated continuously for 5 mo. with thiouracil. BMR fell to normal 31 days after initiation of treatment. Initially he received 900 mg. daily for 3 days, followed by 300 mg. for 14 days and then 100 mg. for 21 days. During the last few days of this period a mild relapse occurred, apparently due to too rapid reduction of the dose of thiouracil. The dose was increased to 300 mg. daily. Thyrotoxicosis subsided and after 14 days the dose was reduced to 200 mg. daily. This dose was continued for 19 days and then reduced to 100 mg. daily for 50 days. Finally he received 50 mg. daily for 40 days. After 5 mo. of continuous treatment, the gland had increased considerably in size and, in spite of a disappearance of thyrotoxicosis, a surgical consultant insisted upon thyroidectomy. At the present time, 5½ yr. following thyroidectomy, he is 18 yr. old, is undersized and has required continuous treatment with dessicated thyroid gland for post-operative hypothyroidism.

Case 3. Classified severe. R. F., a Negro female, 13 yr. of age, was treated for a total of 26 mo. She received thiouracil for 6 mo., propylthiouracil for 18 mo. and, following a relapse after a 5½ mo. remission, methylthiouracil for 2 mo. BMR fell slowly and did not reach normal until after 180 consecutive days of thiouracil and 91 days of propylthiouracil—a total of 271 days. Initially she received thiouracil, 300 mg. daily for 16 days, 250 mg. for 10 days and 200 mg. for 5 mo. She was then given propylthiouracil, 250 mg. daily for 28 days, 200 mg. for 28 days, 250 mg. for 26 days and 100 mg. for 2 mo. At this time she developed a severe acute upper respiratory infection followed by a mild relapse. The dose was then increased to 200 mg. daily for 30 days, followed by 100 mg. for 3½ mo. and 50 mg. for 2 mo. A second, more severe relapse occurred at this time apparently due to an emotional shock when her father was killed. The dose was then increased to 200 mg. daily for 30 days followed by 100 mg. for 2 mo. and finally 50 mg. for 3½ mo. Without treatment she experienced a remission for the following 5½ mo. Subsequently, a third and severe relapse occurred for no obvious reason. She was then given methylthiouracil, 300 mg. daily for 21 days, 400 mg. for 25 days and finally 600 mg. for 10 days. In spite of the large doses thyrotoxicosis persisted. Furthermore, the thyroid had increased in size. Methylthiouracil was discontinued and she was given Lugol's solution for 2 wk. at the end of which time a subtotal thyroidectomy was performed. In spite of failure of medical treatment, she was carried through her pubertal period during which time normal growth and sexual development took place. Subtotal thyroidectomy was followed by evidence of mild hypothyroidism for which she received dessicated thyroid gland. At the present age of 16 yr., 6 mo. after thyroidectomy, she appears normal. She is receiving U.S.P. dessicated thyroid gland .06 gm. daily.

Case 4. Classified severe. D. M., a white female, 15 yr. of age, responded poorly during 6 mo. of continuous methylthiouracil therapy. At no time did her BMR fall to normal. She received 200 mg. daily for 45 days and subsequently 300 mg. for 4½ mo. Psychotic episodes occurred and she developed cardiac complications consisting of enlargement, increased tachycardia and gallop rhythm. She was successfully prepared with Lugol's solution over a period of 3 wk. and a subtotal thyroidectomy was performed. At the present time, 2 yr. following thyroidectomy, she is 17½ yr. old and is well.

Case 9. A. L., a white male 10½ yr. of age, was treated for 3 mo. with propylthiouracil. At no time did his BMR fall to normal. He received 200 mg. daily for the 1st 10 days and subsequently a variable daily dose for an additional 2½ mo. Response to treatment was slow, although his BMR dropped from plus 53 to plus 26 during the 1st 2 wk. of treatment. However, cooperation was poor, he took his medication irregularly, he was extremely excitable, and at times unmanageable, so much so that his mother felt that she could not see him through prolonged medical treatment. Propylthiouracil was discontinued, he was given phenobarbital and Lugol's solution and a subtotal thyroidectomy was performed 2 wk. later. At the present age of 13½ yr., almost 3 yr. following thyroidectomy,

TABLE 2

PATIENTS SUCCESSFULLY TREATED WITH THIOUREA DERIVATIVES

No.	Name	Age	Sex	Duration of Treatment	Duration of Remission	Relapses	
						No.	Possible Cause
1	C.D.	9 yr.	F	13 mo.	4 yr.	3	a. Thyroid medication b. Shortage of drug c. Severe URI after a remission of 8 mo.
5	A.M.	11 yr.	F	12 mo.	12 mo.	0	
6	N.G.	9 yr.	F	7 mo.	14 mo.	1	Too rapid reduction of dose
7	C.C.	5 yr.	F	15 mo.	7 mo.	1	Severe URI while on maintenance dose
8	J.G.	13½ yr.	M	6 mo.	3 yr.	0	
			Patients Thyroidectomized				
2	M.K.	12 yr.	M	5 mo.	—	1	Too rapid reduction of dose
3	R.F.	13 yr.	F	26 mo.	5½ mo.	3	a. Severe URI while on maintenance dose b. Emotional shock c. No apparent cause
4	D.M.	15 yr.	F	6 mo.	—		
9	A.L.	10½ yr.	M	3 mo.	—		

TABLE 3

LENGTH OF TIME REQUIRED FOR BMR TO RETURN TO NORMAL FOLLOWING INITIAL TREATMENT

No.	Name	Age	Drug*	Maximum dose of drug (mg.)	Initial BMR %	Days taken for BMR to return to normal
1	C.D.	9 yr.	T	400	43	28
2	M.K.	12 yr.	T	900	49	31
3	R.F.	13 yr.	T	300	32	180 } total 271 days
			P	250		91 }
4	D.M.	15 yr.	M	300	49.6	No improvement after 6 mo.
5	A.M.	11 yr.	P	200	37	10
6	N.G.	9 yr.	P	150	51.9	10
7	C.C.	5 yr.	P	150	46	14
8	J.G.	13½ yr.	P	200	49.3	18
9	A.L.	10½ yr.	P	200	53	Only slight improvement after 3 mo.

* T indicates thiouracil.
P indicates propylthiouracil.
M indicates methylthiouracil.

he still requires dessicated thyroid gland for postoperative hypothyroidism and obesity. Furthermore, he has a large keloid scar for which radiation therapy is contemplated.

Summary

The 5 successfully treated patients (Cases 1, 5, 6, 7 and 8) were treated for 13, 12, 7, 15 and 6 mo. and are in remission for 4 yr., 12 mo, 14 mo., 7 mo. and 3 yr., respectively. The 4 patients operated upon (Cases 2, 3, 4 and 9) were treated for 5, 26, 6 and 3 mo., respectively. Case 3 had a remission for 5½ mo. after 24 mo. of continuous medical treatment, relapsed and became refractory to the drug during 2 mo. of additional treatment. (See table 2.)

In 3 of the 5 successful cases (Cases 5, 6 and 7), BMR returned to normal within 10 to 14 days after initiation of treatment. In 1 case (Case 8), BMR fell to normal after 18 days and in the other (Case 1) after 28 days. In 2 of the unsuccessfully treated cases (Cases 2 and 3), BMR fell to normal after 31 and 271 days, respectively. The BMR of 2 cases (Cases 4 and 9) failed to return to normal. (Table 3.)

Relapses occurred from 1 to 3 times in 5 cases. Three patients were in the successfully treated group (Cases 1, 6 and 7) and 2 in the operated group (Cases 2 and 3). These relapses apparently resulted

TABLE 4

Patients Thyroidectomized Following Medical Treatment

No.	Name	Sex	Age at onset of treatment	Duration of medical treatment	Age at time of thyroidectomy	Present age	Present status
2	M.K.	M	12 yr.	5 mo.	12½ yr.	18 yr.	Under treatment for hypothyroidism and retarded growth
3	R.F.	F	13 yr.	26 mo.	15½ yr.	16 yr.	Mild hypothyroidism, improving
4	D.M.	F	15 yr.	6 mo.	15½ yr.	17½ yr.	Normal
9	A.L.	M	10½ yr.	3 mo.	10¾ yr.	13½ yr.	Under treatment for hypothyroidism and marked obesity. Severe keloid scar

from thyroid given in an attempt to reduce the size of the gland (Case 1); insufficient treatment due to shortage of the drug (Case 1); too rapid reduction of the therapeutic dose (Cases 2 and 6); severe acute upper respiratory infections: 1 after the patient had been in a remission for 8 mo. without therapy (Case 1) and 2 while the patients were on maintenance therapy (Cases 3 and 7); and emotional shock (Case 3). (Table 2.)

Subtotal thyroidectomy was performed on 4 patients because of: (1) markedly enlarged thyroid (Case 2), (2) refractoriness to the drug during treatment following a third relapse (Case 3), (3) slow response, psychotic episodes and cardiac complications (Case 4) and (4) poor cooperation, patient unmanageable (Case 9).

In the group operated upon, 3 of the 4 subsequently developed endocrine disturbances. One became moderately hypothyroid and retarded in growth (Case 2), 1 mildly hypothyroid (Case 3) and 1 moderately hypothyroid and markedly obese (Case 9). Up to the present time all have required continuous treatment with dessicated thyroid gland to correct the hypothyroidism. One patient has a severe keloid scar (Case 9). (Table 4.)

The blood counts showed no significant changes. Usually there was a mild to moderate reduction in the granulocytes with a relative increase in the lymphocytes. A mild eosinophilia was observed in 2 cases. There were no changes in the erythrocyte counts or hemoglobin that could be attributed to drug therapy. No hemorrhagic tendencies developed and there was no clinical evidence of jaundice in any of the patients.

At no time has there been any evidence of hypothyroidism in any of the 5 patients who are in remission following medical treatment.

Discussion

In a recent report on the treatment of hyperthyroidism in children with thiouracil, Williams and Janney[8] emphasized the importance of a trial of conservative management of hyperthyroidism in children. They stated that the disease usually develops more rapidly and may be less severe in the child and in some instances decreases in severity with age. Consequently, conservative management may either prevent unnecessary thyroidectomy or defer operation until after puberty when growth and development become mature and stabilized. They treated 6 female children, 7 to 14 years of age. Satisfactory response was obtained in all the cases. Minor relapses were readily controlled by curtailing activity and increasing the dose of the drug or resumption of treatment. At the time of their report, the periods of observation were too short to evaluate the cases as to the permanency of cure.

Recently, Bartels[3] reviewed the results of treatment of hyperthyroidism with propylthiouracil at the Lahey Clinic and discussed the arguments for and against prolonged medical management. He is of the opinion that propylthiouracil alone is not curative for primary hyperthyroidism in most cases, particularly the moderate and severe cases with large goiters. He also states that patients have to be under observation continuously, to which many object and would rather undergo an operation. Reactions occur in 1.8 to 2% and possible histopathologic changes occur in the thyroid as a result of treatment.

Bartels[4] reported that thyroidectomy was performed on the 12 children among the first 1000 patients with hyperthyroidism to receive antithyroid treatment at the Lahey Clinic in preparation for thyroidectomy. The postoperative convalescence of 10 patients was uneventful; in two patients, a tracheotomy was necessary. These were two children who were over-treated and developed myxedema, a condition now avoided by more careful regulation of the dose of the antithyroid drug. Follow-up studies have been carried out on 11 patients for a period of 6 months to 3 years. One child who had an adenomatous goiter and developed myxedema requires continuous thyroid medication. Two patients developed recurrent goiter, one with hyperthyroidism. Eight patients are in excellent condition.

Recently, Jackson and Haley[9] treated eight children ranging in age from 8 to 16 years with thiourea derivatives. Of the eight, one "has remained well," in one the disease was arrested, contact with one patient was lost after discontinuing medication because of a toxic rash, and one patient was still under treatment. Her thyrotoxicosis was controlled but the thyroid was enlarged. Four have undergone subtotal thyroidectomy: one patient received a right lobectomy and isthmectomy and three months later a left lobectomy after discontinuing thiouracil because of a toxic rash 2½ months after initiating therapy. Symptoms recurred five months later and were controlled by propylthiouracil given for 11 months. However, because of an enlarged right upper lobe of the thyroid, a third operation was performed. There was no follow-up history. One patient was operated upon because of an enlarged thyroid although thyrotoxicosis was controlled after eight months of propylthiouracil therapy. Eighteen months after operation her basal metabolic rate was plus 29 and she required a reducing diet. One patient was operated upon following a relapse one month after stopping medication consisting of 10 days of thiouracil and six months of propythiouracil. One year after operation she appeared well but was given

Lugol's solution because her basal metabolic rate was plus 35. One patient was operated upon for a large hyperplastic intrathoracic goiter. Propylthiouracil was discontinued after two weeks because of a leukopenia. She was receiving a reducing diet. On the basis of their experience with these cases, Jackson and Haley[9] believe that individual response to antithyroid drugs is uncertain in children and their place probably is in preoperative preparation or in patients in whom it may be necessary to delay operation. They emphasized that depression of the white blood cells must be watched for, although there were no serious complications in their cases. Also, the goiterogenic action of the thiourea derivatives was responsible for thyroidectomy in two of their cases.

In spite of the fact that cure of thyrotoxicosis with thiourea derivatives alone is unpredictable, there are problems and circumstances incident to childhood which justify prolonged medical treatment of thyrotoxicosis in many instances. Even in the hands of skillful surgeons the possibility of undesirable postoperative effects on growth and endocrine function is real. As Topper[1] states, "the question of the amount of thyroid tissue to be removed is always problematic, since future demands on the gland are unpredictable." Furthermore, endocrine balance is more easily disturbed in childhood and may be difficult to control with endocrine therapy. During the past several years the authors had under their care five thyroidectomized children (not included in the present study) who developed postoperative endocrine disturbances: retarded growth, hypoparathyroidism, hypothyroidism and polyglandular disturbances including retarded sexual development and obesity. All required prolonged endocrine therapy. In the present group, 3 of the 4 thyroidectomized children showed endocrine disorders, viz., hypothyroidism and retarded growth, hypothyroidism, and hypothyroidism and obesity—all requiring prolonged treatment with dessicated thyroid gland. Because of the possibility of such disturbances, it is believed that thyroidectomy should be avoided if possible.

As Williams[10] recently stated, treatment with thiourea derivatives is relatively simple and inexpensive and is not associated with paralysis of vocal cords, hypoparathyroidism or permanent myxedema. He also stated that subtotal thyroidectomy is the treatment of choice primarily when a large nodular gland is present or when a rapid recovery is one of the main objectives. Of the 119 adult cases who received prolonged treatment with thiourea derivatives, reported by Williams,[10] 57 (48%) had remissions for periods of from 1.5 to 4.5 years. Four (44.4%) of the present authors' patients had remissions for periods of from 1 to 4 years and one is well at present after going into her eighth month of remission. We agree that individuals with small goiters and those with mild thyrotoxicosis have the best opportunity for permanent remission.

Prolonged medical treatment in children usually does not impart the economic hardships that it does with adults who may have to take time away from their jobs and thus jeopardize their livelihoods. The problem of prolonged follow-up with frequent visits to the doctor usually offers no difficulty. Parents and patient are usually cooperative. The exception occurs as in the case of A.L. (Case 9), who became unmanageable while under treatment.

In the nine cases in this series, no significant untoward reactions occurred in spite of the large doses used. Mild to moderate leukopenia in several instances did not require discontinuation of treatment. However, the possibility of more severe reactions, such as liver damage[11] and agranulocytosis,[11-13] should be kept in mind and the blood and urine should be examined every 2 to 3 weeks while the drug is being administered.

Conclusions

In weighing the advantages of one method of treatment over the other, no one procedure is the treatment of choice in all instances. Each patient must be considered individually. As a result of an experience with nine cases of thyrotoxicosis in children, it is the authors' opinion that prolonged medical treatment with thiourea derivatives is the initial treatment of choice in many patients. There is the possibility of permanent cures in some. In others, remissions may last sufficiently long to carry the child through puberty and thus lessen the possibility of growth and other endocrine disturbances that may develop as a result of thyroidectomy during childhood. In the event thyroidectomy becomes necessary, following failure of initial medical treatment or after repeated relapses, it is not likely that the patient's health has been jeopardized.

This series of cases is not large enough to draw conclusions as to how long these patients should be treated, and not sufficient time has elapsed to form definite opinions as to the possibility of permanent cures. Nevertheless, from observations up to the present time, it requires from 6 to 12 months or longer of continuous treatment to produce a remission. It is believed that two of these patients (Cases 1 and 8) who have been in a remission for 4 and 3 years are cured.

Factors determining the length of treatment are the severity of the case, including the degree of thyroid enlargement, the speed of initial response, and the occurrence of relapses requiring increase in dose or resumption of treatment. The less severe cases respond more rapidly, require shorter periods of prolonged treatment, and are more likely to experience a permanent cure.

Relapses may occur due to acute infectious disease, emotional trauma, too rapid reduction of the therapeutic dose of the drug, too short a period of therapy, or the administration of dessicated thyroid gland administered in an attempt to reduce the size of the thyroid. However, in the cases reported here, relapses were not as severe as the initial illness and responded well to increase in dosage or resumption of treatment. The exception occurred in one patient who eventually became refractory to the drug after a third relapse.

It is not uncommon for goiters to increase in size during the early weeks of treatment, particularly when large doses of the drug are given. Eventually, however, most of them decrease over a period of months.[9] This is particularly true of the slightly and moderately enlarged thyroids with corresponding degrees of thyrotoxicosis and less true of the large thyroids with severe thyrotoxicosis.

In those instances where the thyroid fails to decrease in size, or decreases slowly, and the patient is under maintenance therapy or in a remission, the administration of from .015 to .03 gm. of dessicated thyroid gland daily may result in a further decrease in size of the gland. This is apparently due to the antagonistic action of the thyroid to the secretion of pituitary thyreotropic hormone, the latter being responsible for thyroid enlargement.[9]

In most cases that responded favorably, exophthalmos receded completely or partially. However, exophthalmos was not severe in any of these patients.

Summary

Nine children with thyrotoxicosis whose ages ranged from 5 to 15 years have been treated with thiourea derivatives during the past six years.

Four subsequently underwent subtotal thyroidectomy. Three of the four developed

endocrine complications, viz., hypothyroidism and retarded growth, mild hypothyroidism, and hypothyroidism and marked obesity.

At the present time, 5 patients are in remission for periods of from 7 months to 4 years.

From 1 to 3 relapses occurred in 5 patients who experienced remissions. Up to the present time, only one of these has undergone thyroidectomy.

No untoward symptoms resulted from the drugs used in any of the patients.

The advantages of prolonged medical treatment of thyrotoxicosis in children is discussed.

ACKNOWLEDGMENTS

The authors are indebted to Dr. F. Basch for permission to report Case 6 and to Dr. Benjamin Kagan, Director of Pediatric Research, Sarah Morris Hospital, for helpful suggestions in the preparation of this manuscript.

REFERENCES

1. Topper, Anne, Treatment of exophthalmic goiter in childhood: Report of follow-up study in 12 cases, Am. J. Dis. Child. **76**:26, 1948.
2. Wilkins, L., Toxic goiter, in Holt's Diseases of Infancy and Childhood, ed. 11, revised by L. E. Holt, Jr., and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1941, p. 701.
3. Bartels, E. C., Appraisal of goiterogens: Results of treatment with thiouracil, propylthiouracil and related antithyroid drugs, J. Clin. Endocrinol. **8**:766, 1948.
4. Bartels, E. C., Hyperthyroidism in children, Lahey Clin. Bull. **6**:68, 1949.
5. Cameron, A. T., Graves' disease in children and adolescents, in Recent Advances in Endocrinology, Philadelphia, The Blakiston Company, 1949, p. 76.
6. Reilly, W. A., Thyrotoxicosis, Am. J. Dis. Child. **60**:79, 1940.
7. McIntosh, C. B., Treatment of hyperthyroidism in children, J. Pediat. **25**:133, 1944.
8. Williams, L. P., and Janney, F. R., Thiouracil in childhood hyperthyroidism, J. Pediat. **30**:370, 1947.
9. Jackson, A. S., and Haley, H. B., Exophthalmic goiter in children: Treatment with propylthiouracil, Am. J. M. Sc. **218**:493, 1949.
10. Williams, R. H., Selection of therapy for individual patients with thyrotoxicosis, J.A.M.A. **139**: 1064, 1949.
11. Livingston, H. J., and Livingston, S. F., Agranulocytosis and hepatocellular jaundice: Toxic reactions following propylthiouracil therapy, J.A.M.A. **135**:422, 1947.
12. Eisenmenger, W. J., and Steele, J. M., Leukopenia following use of propylthiouracil, J.A.M.A. **135**:510, 1947.
13. Davis, H., Jr., and Murphy, F. J., Leukopenia and drug fever in juvenile hyperthyroid treated with propylthiouracil, Clin. Proc. Child. Hosp., Washington, D.C. **5**:286, 1949.

SPANISH ABSTRACT

El tratamiento del hipertiroidismo en niños con derivados de la thiourea

Se reportan nueve casos de hipertiroidismo en niños entre 5 y 15 años de edad tratados con los derivados de la thiourea. Tiroidectomia subtotal fué realizada subsequentemente en cuatro casos de los cuales tres desarrollaron complicaciones endocrinas vg: hipotiroidismo con retardo del desarrollo; ligero hipotiroidismo y hipotiroidismo con obesidad marcada respectivamente.

Al momento presente cinco pacientes continuan en remision por periodos que oscilan entre 7 meses y 4 años. Relapsos han ocurrido en cinco pacientes que experimentaron remisiones con el tratamiento medico pero solamente un caso ha necesitado la tiroidectomia.

No hubo sintomas toxicos durante la administracion de las drogas en los casos reportados.

Los autores discuten los beneficios del tratamiento medico prolongado en niños con hipertiroidismo.

104 South Michigan Boulevard

STUDIES OF THE CARDIOVASCULAR AND RENAL SYSTEMS IN THE NEWLY BORN INFANT USING FLUORESCEIN

I. Circulation Time Immediately after Birth

By LAWRENCE B. SLOBODY, M.D., GEORGE D. ROOK, M.D., MORRISON LEVBARG, M.D., AND MADELAINE MORCY, M.D.
New York City

FLUORESCEIN has been used in the adult to study circulation time, capillary permeability and renal excretion. Similar studies have been undertaken in the newborn infant because of the simplicity of technics involved and low toxicity of the chemical. Data are being collected on circulation times in normal and abnormal newborn infants, on renal excretion of fluorescein in the early postnatal period as compared with later infancy and childhood, and on capillary permeability utilizing the dermofluorometer method. This report presents the results of studies of circulation time done immediately after birth.

Lange and Boyd,[1] in 1942, described the fluorescein method of determining the circulation time. They injected fluorescein solution 5% alkalinized with 5% sodium bicarbonate into the antecubital vein and timed its arrival in the lips by the greenish-gold fluorescence this substance emits under long wave ultraviolet light (3600-4000 Angstrom units). Fluorescein fulfils all the requirements of the perfect chemical substance for determination of the circulation time as set forth by Robb and Weiss.[2] 1. It is nontoxic in the dose employed. 2. It does not influence the velocity of blood flow. 3. It is rapidly inactivated so that tests may be repeated if desired. 4. The signal reaction is objective and readily discernible in both normal and pathologic conditions. In addition, the low cost of the drug, the simplicity of the technic and accuracy of the results make fluorescein the chemical of choice.

The first fluorescein circulation time determinations in children were done by Witzberger and Cohen[3] in 1943. Gasul et al.[4] reported studies in infants and children utilizing the same substance and Winsor et al.[5,6] had used the fluorescent property of riboflavin to study blood velocity. At present, fluorescein is used routinely for the determination of circulation time.

Despite all these clinical experiences, no exact data on the circulation time of the newborn infant have been available. Such factors as the early instability, high mortality and the poor resistance to infection have limited investigation with this age group. The technical difficulties of introducing a substance into the small veins and the necessity of obtaining a purely objective response are additional problems peculiar to the study of the

---

From the Department of Pediatrics of New York Medical College, Flower and Fifth Avenue Hospitals, and the Metropolitan Hospital, Department of Hospitals, New York City.

Supported by a grant from the New York Heart Association, Inc.
(Received for publication Dec. 3, 1949.)

newborn infant. The youngest patient tested by Winsor et al.[5,6] was 14 days old. Gasul et al.[4] included a 15 day old infant in their series. Hubbard and his co-workers,[7] utilizing radioactive sodium, determined the left arm-to-right arm circulation time in a child 6 weeks of age. Haselhorst's approach to the problem was entirely different.[8] He attempted to study the newborn circulation time by injecting Congo red into the umbilical vein while the cord was still pulsating, and then collecting samples of blood when the dye reappeared in the vein. Clement A. Smith,[9] on comparing Hubbard's results (3 to 12 sec.) with those of Haselhorst (30 to 60 sec.), states, "There is so much difference between these figures and those for the infant (and placenta) at birth that data obtained by some method such as the use of radioactive material in infants on the first or second day would be most welcome. The difficulties of using any method are obviously great."

The following data summarize the results of umbilical vein- or ductus venosus-to-lip circulation time in 90 apparently normal newborn infants using the fluorescein technic (table 1).

Plan of Study

The materials used in this study were fluorescein* 5% solution alkalinized with 5% $NaHCO_3$, a filtered ultraviolet light emitting only long waves (3600-4000 A.U.), polyethylene tubing (0.038 ID and 0.047 ID†), and a stop watch calibrated in 0.1 sec.

The subjects were all normal newborn infants delivered at term, except for 3 prematures in excellent condition. All infants requiring unusual resuscitative efforts for the onset of respiration were excluded, as were those with any recognizable anomaly.

The subjects were removed to a special room as soon after delivery as was feasible. All trials were run within 2 hr. of delivery except for 2 cases, 1 done on a 125 minute old infant and the other on a 140 minute old infant. The temperature of this room, which could be completely darkened, was maintained at about 27°C. to prevent chilling during the procedure. The umbilical cord, which was always ligated at least 15 cm. from the skin at the time of delivery, was clipped to a length of approximately 5 cm. There was little bleeding, the umbilical vein oozing only slightly at times. A section of polyethylene tubing, measuring about 10 cm., washed free of the zephiran® in which it was kept, was then inserted into the umbilical vein. In the 1st 45 cases the distal end of the tubing was placed in close approximation to the skin, therefore still in the umbilical vein. In the remaining 45 cases, the tube was advanced at least 3 cm. below the skin into the ductus venosus. Back-flow of blood was considered proof that the tubing was in the proper place. The 0.047 ID tubing was used in the last 17 cases and is the size recommended for cord catheterization, because its greater firmness facilitates passage through the umbilical vein.

With the tube in position, an 18 or 19 gauge 2.5 cm. needle attached to a tuberculin syringe containing the desired amount of fluorescein solution was inserted into the proximal end. The room lights were then extinguished and the ultraviolet light was directed into the subject's face. At a given signal the fluorescein was injected rapidly as the stop watch was started. With the first appearance of fluorescence of the lips the watch was stopped. The interval measured was considered the umbilical vein- or ductus venosus-to-lip circulation time, depending on the position of the tube. Varying amounts of fluorescein were used for the determinations. In the 1st 16 cases, 0.21 ml. of the 5% solution was injected for each trial, thus approximating the dosage of 0.07 ml./kg. body weight suggested by Witzberger and Cohen. In the next 10 cases the same amount of fluorescein diluted with an equal amount of isotonic saline was injected. The following 10 cases had circulation time determinations with only 0.09 ml. of the 5% fluorescein solution. For the remaining 48 cases, 0.1 ml. of the standard fluorescein solution was used.

The exact time elapsing between obstetric delivery and injection of the dye was noted for each case. The degree of activity during the procedure, classified in 1 of 3 groups, quiet, active or active and crying, was recorded also for each subject.

---

* Manufactured by C. F. Kirk Co., New York City, as fluorscite®.

† Internal diameter in inches.

TABLE 1

CIRCULATION TIMES IN NEWBORN INFANT

No.	Sex	Wt. kg.	Color	Technic	Amount of Fluorescein ml.	Circulation Time sec.	Age min.	Activity of Child
1	f	2.92	NW	polyethylene tubing. .038 ID inserted into umbilical vein.	0.21	4.9	17	quiet
2	f	2.57	W	"	"	5.0	45	quiet
3	m	2.98	NW	"	"	4.6	25	active and crying
4	m	3.16	W	"	"	5.0	70	quiet
5	m	3.50	NW	"	"	4.8	50	quiet
6	m	3.73	NW	"	"	4.6	20	quiet
7	m	4.31	W	"	"	4.6	55	quiet
8	m	3.69	NW	"	"	4.8	.38	quiet
9	m	2.04	W	"	"	4.7	50	active
10	m	3.09	NW	"	"	4.4	125	active
11	m	2.38	NW	"	"	5.5	20	active and crying
12	m	3.66	W	"	"	4.8	140	quiet
13	f	3.35	NW	"	"	5.0	24	active and crying
14	f	2.30	W	"	"	7.0	40	quiet
15	m	3.09	NW	"	"	4.2	15	active
16	f	2.65	NW	"	"	4.1	60	active and crying
17	m	2.68	NW	"	0.21 & 0.21 ml. saline	5.2	20	quiet
18	f	2.67	NW	"	"	4.8	74	quiet
19	m	3.20	NW	"	"	4.8	70	quiet
20	f	3.74	NW	"	"	5.8	80	quiet
21	f	3.10	NW	"	"	4.8	45	quiet
22	m	2.98	NW	"	"	5.0	32	quiet
23	m	3.54	NW	"	"	5.0	32	active
24	m	2.78	NW	"	"	5.0	18	active
25	m	3.87	NW	"	"	6.0	43	active and crying
26	m	3.98	NW	"	"	4.7	22	active and crying
27	m	3.09	W	"	0.09	4.6	30	active and crying
28	f	2.82	NW	"	"	6.5	20	quiet
29	f	2.84	NW	"	"	4.9	46	active and crying
30	f	3.61	NW	"	"	4.4	23	active
31	f	2.82	NW	"	"	4.4	80	quiet
32	m	3.00	W	"	"	5.0	35	quiet
33	m	3.31	NW	"	"	4.2	40	quiet
34	f	2.89	NW	"	"	4.7	23	active and crying
35	m	3.07	NW	"	"	5.0	36	active and crying
36	m	2.98	W	"	"	4.5	30	active
37	m	3.27	NW	"	0.10	4.8	32	active
38	f	2.87	NW	"	"	7.0	30	active
39	f	3.67	W	"	"	4.1	26	active
40	m	3.32	NW	"	"	5.0	10	active
41	m	3.13	W	"	"	3.4	38	quiet
42	m	3.22	NW	"	"	5.0	85	quiet
43	f	2.95	W	"	"	3.4	50	quiet
44	f	3.52	NW	"	"	4.3	20	active and crying

TABLE 1—*Continued*

No.	Sex	Wt. kg.	Color	Technic	Amount of Fluorescein ml.	Circulation Time sec.	Age min.	Activity of Child
45	m	3.67	NW	"	"	3.1	25	active and crying
46	m	3.35	NW	Tube in ductus venos.	0.10	4.0	34	active and crying
47	m	3.84	NW	"	"	4.0	70	active and crying
48	f	3.23	NW	"	"	4.2	40	active and crying
49	f	3.02	NW	"	"	4.8	50	active and crying
50	m	3.30	W	"	"	4.2	21	active and crying
51	f	3.91	NW	"	"	4.1	50	quiet
52	f	3.13	W	"	"	5.4	55	active
53	m	3.35	NW	"	"	4.0	34	active and crying
54	f	3.02	W	"	"	5.4	85	quiet
55	m	3.35	W	"	"	5.0	65	quiet
56	m	3.55	W	"	"	4.8	28	active and crying
57	m	3.29	W	"	"	4.4	70	active
58	m	3.35	W	"	"	5.8	80	quiet
59	f	2.95	NW	"	"	5.0	75	active and crying
60	f	3.90	NW	"	"	5.5	80	active
61	f	3.02	NW	"	"	4.0	35	quiet
62	m	2.58	W	"	"	4.4	25	quiet
63	m	3.77	NW	"	"	4.2	40	active
64	f	2.85	NW	"	"	4.8	30	active and crying
65	f	2.72	W	"	"	4.9	70	active and crying
66	m	2.41	NW	"	"	4.6	38	quiet
67	f	2.75	W	"	"	4.1	60	quiet
68	f	3.40	NW	"	"	4.2	15	active and crying
69	f	2.74	W	"	"	4.8	73	quiet
70	m	3.09	W	"	"	4.2	28	quiet
71	m	3.67	W	"	"	4.3	30	quiet
72	m	2.79	W	"	"	3.8	27	quiet
73	m	2.96	W	"	"	3.6	25	quiet
74	m	2.95	W	Tube in ductus venos. .047ID	"	5.0	50	quiet
75	m	4.49	W	"	"	4.0	40	active and crying
76	f	3.02	NW	"	"	4.0	20	active and crying
77	m	3.43	NW	"	"	4.1	19	active
78	f	2.99	W	"	"	3.5	27	active
79	m	2.70	NW	"	"	4.5	40	active and crying
80	m	2.50	NW	"	"	3.3	20	quiet
81	m	3.40	W	"	"	4.2	28	active
82	m	3.47	NW	"	"	4.0	31	quiet
83	f	4.03	NW	"	"	4.6	15	quiet
84	m	4.08	NW	"	"	4.0	34	active and crying
85	m	3.35	NW	"	"	4.1	72	active and crying
86	f	3.40	W	"	"	5.0	60	quiet
87	f	3.49	NW	"	"	4.2	14	quiet
88	f	3.74	W	"	"	6.0	20	active
89	f	3.13	W	"	"	5.0	20	active
90	m	3.37	NW	"	"	4.0	10	quiet

Results

The umbilical vein-to-lip circulation time was determined in 45 newborn infants. The mean circulation time was 4.8 ± 0.7 sec. with a range of 3.1 to 7.0 sec. The varying amounts of fluorescein used in this group had no effect on the determinations, the fluorescence of the lips being observed as easily with the smaller doses.

The ductus venosus-to-lip circulation time was determined in 45 newborn infants. The mean circulation time was 4.4 ± 0.6 sec., with a range of 3.3 to 5.8 sec.

The results for both groups, umbilical vein-to-lip and ductus venosus-to-lip, were analyzed to determine the relationship, if any, between the circulation time and length of time after delivery that the tests were performed (table 2). In the first group, the

TABLE 2

Relationship of Age to Circulation Time

Time between Delivery and Procedure min.	Circulation Time					
	Umbilical Vein-to-Lip			Ductus Venosus-to-Lip		
	No. of cases	Average sec.	Range sec.	No. of cases	Average sec.	Range sec.
Delivery to 30	19	4.8	3.1 to 7.0	19	4.3	3.3 to 6.0
31 to 60	18	4.8	3.4 to 7.0	16	4.4	4.0 to 5.4
61 to 120	6	4.9	4.4 to 5.8	10	4.9	4.0 to 5.8
Over 120	2	4.6	4.4 to 4.8			

time following delivery at which the test was done seemed to have little influence on the circulation time, for the results were almost identical. The ductus venosus-to-lip group of cases did show slight variations that probably are not statistically significant.

It will be noted that of the seven circulation times below 4 sec., five were obtained during the first half hour of life and two, during the second half hour. Five of this group of seven infants were re-examined at 6 weeks of age and were found to be asymptomatic. There was no cyanosis present and no heart murmurs were heard.

The activity of the infants was noted during the procedure. Each was placed in one of three categories: quiet, active or active and crying. There were 42 infants in the "quiet" category; 20 were classed as "active," and 28 as "active and crying." In correlating activity with the circulation time, the three groups were almost identical; the "quiet" infants had a mean circulation time of 4.7 sec. (range 3.4 to 7.0 sec.), as had the "active" infants (range 3.5 to 7.0 sec.), while the "active and crying" infants averaged 4.5 sec. (range 3.1 to 6.0 sec.).

There was no apparent relationship between the circulation time and sex, color or weight. The three premature infants included in this series had circulation times close to the average. Two had umbilical vein-to-lip times done and these were found to be 4.7 sec. and 5.5 sec. With the third, a ductus venosus-to-lip time was 4.6 sec.

Comments

In previous studies, it had always been noted that the younger the age group, the faster the circulation time. The circulation time results recorded here are lower than any previously reported, thus following the general rule, but are not directly comparable because of the age group and the entirely different segment of circulatory pathway measured. Only

Haselhorst attempted studies in the newborn infant and, as mentioned before, the use of Congo red proved entirely unsatisfactory. He also used a different pathway, umbilical vein-back-to-umbilical vein through the fetus and placenta.

A few studies have been done with young infants (table 3). All these infants were 1 month of age or over, except for two, one 14 days old and the other, 15 days old. Gasul et al., utilizing the fluorescein method, found an arm-to-lip circulation time of 4.5 sec. in the 15 day old infant. The interauricular septal defect present in this infant should not have altered the normal arm-to-lip time. Winsor et al., using riboflavin, did an arm-to-lip test in the 14 day old normal infant, but combined all their statistics in a 14 day

TABLE 3

PREVIOUS STUDIES ON CIRCULATION TIMES IN INFANCY

Investigations	Yr.	Test Substance	Distance Measured	No. of Cases	Age Mo.	Circulation Time	
						Range Sec.	Ave. Age Sec.
Seckel[12]	1931	Histamine	AC. V-to-face	30	1 to 24	14.0 to 17.0	
Haselhorst[8]	1932	Congo red	U.V.-to-U.V.	50	Newborns	30.0 to 60.0	
Hubbard, Preston and Ross[7]	1942	Radioactive Sodium	AC. V-to-Brachial artery of other arm	14	1½ to 22	3.0 to 12.0	7.0
Witzberger and Cohen[3]	1943	Fluorescein	AC.-to-lip	25	1 to 24	5.0 to 9.1	7.0
Winsor, Adolph, Ralston and Leiby[5]	1947	Riboflavin	AC. V-to-lip	15	½ to 71	6.2 to 15.1	8.9
Gasul, Marino and Christian[4]	1949	Fluorescein	AC. V-to-lip	50	4 to 24	5.0 to 8.5	6.5
Kerpel-Fronius and Varga[13]	1949	Congo red	AC. V-to-AC. V of other arm		up to 6	13.0 to 20.0	15.0

AC. V—Antecubital Vein
U.V. —Umbilical Vein

to 5.9 year group and did not give the circulation times obtained in individual tests. However the minimum circulation time recorded was as low as 6.2 sec. Witzberger and Cohen reported on two infants 1 month of age. They had arm-to-lip circulation times of 5 and 6 sec.

All previous workers with fluorescein have reported vomiting as occurring in as high as 5% of cases. Among the 90 infants tested and reported on here, there was no vomiting or other untoward reaction. This may have been due to the small dose of fluorescein used in the majority of cases. Lange and Boyd recommended using a 5% solution 0.07 ml./kg. and this dosage was employed by Witzberger and Cohen. The same amount of drug was used in the first 26 cases reported here. Winsor et al. recommended 5.4 mg./kg. of fluorescein (5% solution 0.11 ml./kg.). An even larger amount was used by Gasul et al., 5% solution 0.15 ml./kg. (0.7 ml./10 lb.). From the results obtained in the present study, it is believed that a 5% solution of fluorescein 0.1 ml. (about 0.03 ml./kg.) is sufficient to give an accurate signal reaction. Even with Negro infants, who have a degree of natural fluorescence, this amount of fluorescein was found to be satisfactory. Diluting the solution to obtain a greater volume of injectable tracer substance did not alter the accuracy of the test.

The umbilical vein is a thin-walled vessel extending about 2 cm. below the skin. Here it joins with the right branch of the portal vein to form a sinus. Intrahepatic vessels are given off by the umbilical vein before this union. The ductus venosus arises from the union of this sinus with the left branch of the portal vein. It is approximately 2 to 3 cm. long with a diameter of 2 to 4 mm. It runs into the vena cava either directly or by the union with the left hepatic vein just before the latter itself joins the inferior vena cava. During the first week of postnatal life there is an infiltration by connective tissue of the lumen of the umbilical vein in the vicinity of the umbilicus, but deeper, this vessel and the ductus venosus remain patent for two to eight weeks.

There was never any great difficulty in inserting the polyethylene tubing, especially when the 0.047 ID was used, nor was this procedure followed by any untoward event. Infection or hemorrhage did not occur in any case. When the cord was cut 5 cm. from the skin only slight oozing from the umbilical vein was noted. The arteries never bled. Apparently there is vasoconstriction and physiologists have attributed this to the increase in oxygen tension, the fall in temperature and the mechanical manipulation of the cord. The clotting mechanism plays little part here. The entire length of the umbilical vessels probably is constricted, for until the tube had been inserted approximately 2½ cm. below the skin and therefore into the ductus venosus, there was never any backflow of blood. The tube was probably never inserted far enough to reach the inferior vena cava. Although the propelling force was supplied by the injection, because of the small amount of fluorescein used and therefore the short distance for the plunger of the syringe to travel, it was felt that the force and speed of the injection itself was not a variable factor in the final determination of the circulation time.

Clement A. Smith states that, "Although the time varies, only about 3 hours (and sometimes very much less) seem to be required for transforming a circulation which functions like a fetal circulation to one which—whatever be the anatomical state of its passages—functions like an adult circulation." Scammon[10] reported that the foramen ovale closes with the first respiration. Barclay, Barcroft et al.[11] have demonstrated the closure of the ductus arteriosus in animals within four minutes following the ligation of the cord. As noted, only 7 of our 90 cases had circulation times below 4 sec.; 5 were obtained during the first half hour of life and 2 during the second half hour. This may indicate that, in most cases, the transformation from the fetal type of circulation to the adult form takes place with the first respiration, while in a small percentage, this change may take place a little later, but still during the first hour of life. Further study is needed on this phase of physiology of the newborn infant.

Cyanosis occurs frequently in the newborn infant. Occasionally it is difficult to determine its etiology. The circulation time should aid in the differentiation of those cases which are of cardiac origin.

Summary

The circulation time with fluorescein has been determined in 90 normal newborn infants immediately after birth.

The umbilical vein-to-lip time was determined in 45 newborn infants. The mean circulation time was 4.8 ± 0.7 sec. with a range of 3.1 to 7.0 sec. The ductus venosus-to-lip time was determined in 45 newborn infants. The mean circulation time was 4.4 ± 0.6 sec. with a range of 3.3 to 5.8 sec.

Polyethylene tubing 0.047 internal diameter and 5% fluorescein 0.1 ml. in 5% sodium

bicarbonate solution are recommended for the determination of circulation time in the newborn infant immediately after birth.

This determination is simple and accurate and may aid in the differential diagnosis of cyanosis of the newborn infant.

ACKNOWLEDGMENT

The authors wish to thank Dr. Kurt Lange for his assistance.

REFERENCES

1. Lange, K. (New York), and Boyd, L. J., Use of fluorescein to determine adequacy of circulation, M. Clin. North America **26**:943, 1942.
2. Robb, C. P., and Weiss, S., Method for measurement of velocity of pulmonary and peripheral venous blood in man, Am. Heart J. **8**:650, 1932-33.
3. Witzberger, C. M., and Cohen, H., Circulation time in infants and young children, determined by fluorescein method, J. Pediat. **22**:726, 1943.
4. Gasul, B. M., Marino, J., and Christian, J., Fluorescein circulation time in normal and pathologic conditions in infants and children, including various types of cengenital malformations of heart, J. Pediat. **34**:460, 1949.
5. Winsor, T., Adolph, W., Ralston, W., and Leiby, G., Objective clinical procedure for determination of circulation velocity using fluorescent tracer substances, Am. Heart J. **33**:704, 1947.
6. Winsor, T., Adolph, W., Ralston, W., and Leiby, C., Fractional circulation times using fluorescent tracer substances, Am. Heart J. **34**:80, 1947.
7. Hubbard, J., Preston, W., and Ross, R., Velocity and blood flow in infants and young children, determined with radioactive sodium, J. Clin. Investigation **21**:613, 1942.
8. Haselhorst, G., Ueber Art und Dauer der Blutstroemung in den Nabelschnurgefaessen post partum, Ztschr. f. Geburtsh. & Gynaek. **96**:487, 1929.
9. Smith, C., Physiology of Newborn, Springfield, Ill., Charles C Thomas, Publisher, 1946.
10. Scammon, R., Summary of anatomy of infant and child, in Abt's Pediatrics, edited by I. A. Abt, Philadelphia, W. B. Saunders Company, 1923, vol. 1, p. 257.
11. Barclay, A. E., Barcroft, J., Barron, D. H., and Franklin, K. J., Radiographic demonstration of circulation through heart in adult and in foetus, and identification of ductus arteriosus, Brit. J. Radiol. **12**:505, 1939.
12. Seckel, H., Die normale Blutumlaufsdauer und Kreislaufsgroesse in den ersten beiden Lebensjahren, Jahrb. f. Kinderh. **131**:87, 1931.
13. Kerpel-Fronius, E., and Varga, F., Dynamics of circulation in malnutrition, PEDIATRICS **4**:301, 1949.

SPANISH ABSTRACT

Estudios de los Sistemas Cardiovasculares y Renales en el Recién Nacido Mediante el Uso de la Flurosceina. El Tiempo de Circulacion Immediatemente Después del Nacimiento

Una de las caracteristicas fisicas de la flurosceina es la emission de fluroscencia color verde—oro cuando es expuesta a las ondas largas de luz ultravioleta. El tiempo de circulacion fué determinado en recién nacidos injectandole una solución de flurosceina a traves de un tubo de "polyethylene" insertado en la vena umbilical en 45 casos y en el conducto venoso en otros 45 casos. El tiempo de circulacion fué calculado desde el momento de la administracion de la flurosceina y la aparicion de esta en los labios de los pacientes cuando estos fueron observados con la lampara de luz ultravioleta. El promedio de tiempo de circulacion de la vena umbilical al labio fué 4.8 + — 0.7 segundos con una variacion de 3.1 a 7.0 segundos. El promedio del tiempo de circulacion del conducto venoso al labio fué de 4.4 + — 0.6 segundos con una variacion de 3.3 a 5.8 segundos. Se recomienda el uso de 0.1 cc de flurosceina al 5% diluida en solucion bicarbonato de soda al 5% y administrada a traves de un tubo de "polyethylene" cuyo diametro interno mida 0.047. Esta determinacion es simple y precisa; posiblemente de gran ayuda en el diagnostico diferencial de la cianosis del recién nacido.

New York Medical College, Flower and Fifth Avenue Hospitals

PENICILLIN AND ITS EFFECT IN PRODUCING A PREDOMINANT GRAM-NEGATIVE BACILLARY FLORA IN UPPER RESPIRATORY TRACT OF CHILDREN

By FREDERICK D. HAFFNER, M.D., ERWIN NETER, M.D., AND MITCHELL I. RUBIN, M.D.
Buffalo

IT IS well known that chemotherapeutic agents and antibiotics have characteristic spectra of activity, being effective against certain species of microörganisms only. The suppression of a component of a flora may be followed by the proliferation of microörganisms which previously were held in check by other species, or it may allow accidental contaminants to grow in profusion. Several investigators have reported that treatment with one particular antibiotic may lead to the elimination of the primary pathogen only to be followed by the appearance of some other organism with potential pathogenic properties. Lipman, Coss and Boots[1] have described the changes of the throat and intestinal tract during prolonged oral administration of penicillin. Castex, Capdehourat and Rechniewski[2] reported that in comparison with observations made before the era of the antibiotics and sulfonamide drugs, the gram-negative bacteria in patients with infections of the respiratory tract have increased in frequency and quantity. Weinstein,[3] Stanley,[4] Appelbaum and Leff,[5] as well as Sommer and Favour,[6] have reported on the occurrence of superimposed infections during antibiotic therapy. Furthermore, certain microörganisms may cause more serious infection in the presence of an antibiotic than in its absence. For example, Foley and Winter[7] have described their observations on increased mortality following penicillin therapy of chick embryos infected with Candida albicans.

Routine observation of the nasopharyngeal bacterial flora of children and infants under therapy with penicillin alone or in conjunction with sulfadiazine has revealed the appearance of certain gram-negative bacilli in a substantial percentage of these cases. It was deemed of interest to study the effects of penicillin therapy on the bacterial flora of the nasopharynx and the throat of infants and children acutely ill with respiratory infections and to evaluate, if possible, the clinical significance of a change in the bacterial flora occurring during antibiotic therapy. The results of this study are embodied in this report.

METHODS

Nasopharyngeal and throat cultures were taken prior to, concomitant with, and subsequent to, antibiotic therapy. The nasopharyngeal swab was inserted into the nostril and kept in contact with the posterior nasopharyngeal wall for 30 sec. The material from the nasopharynx and the throat of patients of Series 2 and 3 was then seeded on the following media (1) blood agar, (2) Endo agar, (3) plain agar containing penicillin 0.1 u./ml. and (4) into brain heart infusion broth. Upon incubation of the broth for 24 hr., subcultures were made on Endo agar. The cultures from patients of Series 1 were seeded only on blood agar and in broth, and subcultures on Endo agar were made subsequently.

From the Departments of Pediatrics and Bacteriology of the Children's Hospital and University of Buffalo, School of Medicine, Buffalo.

Supported by a research grant from the New York State Department of Health.
(Received for publication Dec. 14, 1949.)

TABLE 1

INCIDENCE OF CONVERSION TO GRAM-NEGATIVE FLORA

Series	Total no. of cases	Conversion to gram-negative bacillary flora	No conversion	Gram-negative bacillary flora prior to chemotherapy
1	22	22	—	—
2 and 3	68	30	16	22

The penicillin agar was included in order to suppress *in vitro* the penicillin-sensitive microörganisms and thus allow any of the gram-negative bacilli, if present, to grow without any possible potential antagonism by the penicillin-sensitive flora. The experiment thus anticipates *in vitro* what might happen in the patient during treatment with penicillin. The group of gram-negative bacilli, which may thus be found with these particular culture media and technics, comprises the Esch. coli-A. aerogenes group, K. pneumoniae (Friedländer's bacillus), members of the genera Proteus, Alcaligenes and Pseudomonas.

Of the 90 patients included in this study, 42 cases received penicillin exclusively: 35 penicillin in conjunction with sulfonamides; 7 cases penicillin with streptomycin; and 6 cases penicillin with sulfonamides and streptomycin. Penicillin was administered in all cases by intramuscular injection and 10 patients received aerosol penicillin in addition.

INCIDENCE OF CONVERSION TO GRAM-NEGATIVE FLORA DURING PENICILLIN THERAPY

The bacterial flora of the throat and nasopharynx with particular reference to gram-negative bacilli was studied prior and subsequent to the initiation of penicillin therapy.

In a preliminary survey, 22 patients were selected who had developed a predominant gram-negative flora following therapy with penicillin alone or penicillin and sulfonamides. The original cultures showed none of these organisms on blood agar or in broth which was seeded on Endo agar. These cases are represented by Series 1. Following the demonstration of conversion in these selected cases, the study was then extended to a group of 68 consecutive cases of respiratory infection represented by Series 2 and 3. Series 2 includes children of all ages and Series 3 includes only patients under 2 years of age. Table 1 summarizes the data with respect to "conversion" of the entire group of 90 cases.

Of 68 unselected children studied (Series 2 and 3), 30 who did not harbor gram-negative bacilli in either nasopharynx or throat prior to antibiotic therapy acquired them during or following administration of penicillin. Table 2 lists the gram-negative bacteria found in these converted cases. Members of the E. coli-A. aerogenes group were encoun-

TABLE 2

GRAM-NEGATIVE BACILLARY FLORA FOUND IN CONVERTED CASES

	No. of cases	E. coli-A. aerogenes group	Ps. aeruginosa	A. fecalis	K. pneumoniae	Mixture of gram-negative bacilli
Series 1	22	18	5	1	4	6
Series 2 and 3	30	27	9	1	0	7
	—	—	—	—	—	—
Total	52	45	14	2	4	13

tered in 27 cases, 15 of them showed heavy and 12 a moderate growth of these organisms. A large number of Ps. aeruginosa appeared in the cultures of eight of these children and a moderate number in one case. It should be stated that the appearance of these gram-negative bacilli may have been favored by air-borne cross-contamination from other patients on the ward.

In only 16 of the 68 unselected cases did a conversion to a gram-negative bacillary flora fail to occur. In the remaining 22 children of this group gram-negative bacilli were present prior to penicillin therapy (table 1). It should be mentioned, however, that in 13 of these latter 22 children, the number of gram-negative bacilli increased under penicillin therapy. In only two of these cases was a decrease in the number of gram-negative bacilli noted, and in seven there was no significant change.

The time interval between commencement of penicillin therapy and the appearance of the gram-negative flora was within five days in 20 of the 30 cases, and within one week in all but two cases.

Since only one culture from the nasopharynx and one from the throat was taken prior to penicillin therapy, it seemed of interest to determine which of the subsequent cultures revealed the change in the bacterial flora. Of the 30 patients of this group, the "conversion" was noted on the first culture (3 days on the average) following initiation of specific therapy, in 17 cases; on the second culture in 9 cases; and on the third culture in only 4 instances. It is evident, then, that more than half these patients showed the "conversion" of bacterial flora on the first culture following institution of penicillin therapy.

Since vomiting in infants may result in contamination of the nasopharynx with the gram-negative intestinal flora, the data were analyzed for the incidence of vomiting as a possible cause for the conversion. It was found that of 52 patients (Series 1, 2 and 3) who "converted," only 14 (26%) had vomiting prior to conversion and of the 16 patients who had no "conversion," 6 (38%) had vomiting either prior to admission or subsequent to institution of penicillin therapy. It seems unlikely, therefore, that vomiting *per se* was a major factor responsible for the change in the type of microörganisms found during treatment with penicillin.

Of the entire series of 90 cases, 10 patients received aerosol penicillin in addition to intramuscular penicillin. It is interesting to note that all but one of these cases showed conversion to a predominant gram-negative flora. This observation suggests that penicillin administered as aerosol produces a change in bacterial flora of the respiratory tract even more readily than penicillin administered by the intramuscular route alone.

The question arises as to whether sulfonamides, when administered together with penicillin, may prevent this "conversion." For this analysis 43 patients of Series 2 and 3 were available. Fifteen of 22 patients receiving penicillin alone "converted," whereas this occurred in 12 of 21 patients who were treated with penicillin and sulfonamides. It is evident that "conversion" occurred in a substantial number of cases in spite of the addition of sulfonamides to the therapy.

Clinical Results

Following the demonstration of the conversion to a gram-negative bacillary flora in the throat and nasopharynx of a certain number of penicillin-treated patients, it was thought desirable to evaluate the clinical significance, if any, of this phenomenon.

The cases were clinically evaluated using fever, clinical and roentgenologic evidence of lung involvement and "toxemia" as indices of severity. Each of these three features was

TABLE 3

CLINICAL EVALUATION IN RELATION TO CONVERSION

	Fever		Lung Pathology		Toxemia	
	Degree	Days	Degree	Days	Degree	Days
Group with conversion						
*Series 2, 3 (30 cases)	9.3	4.0	10.1	8.8	7.0	4.8
*Series 1 (13 selected cases with 15 admissions)	18.0	9.3	22.0	14.1	20.0	10.9
Group without conversion						
Series 2, 3 (16 cases)	5.8	2.9	5.0	3.6	3.9	2.8
Group with gram-negative flora prior to chemotherapy						
Series 2, 3 (22 cases)	10.8	5.6	10.1	7.5	9.0	6.3

* Series 1: Selected "converted" cases.
Series 2: Unselected group of children of all ages with respiratory infections.
Series 3: Unselected group of children, under 2 yr. of age, with respiratory infection.

appraised in regard to severity and duration employing the following point system. For each degree of maximum fever per day one point was given. The degree of clinical lung involvement was gauged as 0, 1+ and 2+, with 1+ indicating moderate and 2+ severe clinical findings. Likewise, toxemia was judged clinically as 0, 1+, 2+ and 3+ depending on the severity. Then all the figures were added for each individual case and the total for each group obtained. It is realized that this method of evaluation yields only a very rough estimate of the severity of the illness, which may be difficult to interpret. The results of this evaluation are presented in tables 3 and 4.

From table 3 it may be seen that the group of "converted" cases and the group of patients with gram-negative flora prior to chemotherapy showed a more significant degree and a longer duration of clinical infection than the nonconverted group. In Series 1 only 13 of the 22 cases were analyzed since the remaining nine cases did not have respiratory disease.

Table 4 summarizes the data on patients with acute respiratory infections only, in

TABLE 4

CLINICAL EVALUATION OF PRIMARY ACUTE RESPIRATORY INFECTIONS WITH CONVERSION TO PREDOMINANT GRAM-NEGATIVE BACILLARY FLORA

	Fever		Lung Pathology		Toxemia	
	Degree	Days	Degree	Days	Degree	Days
Group with conversion						
*Series 2, 3 (21 cases)	8.1	3.0	8.2	7.3	5.3	3.8
*Series 1 (10 selected cases)	16.0	7.8	20.0	10.8	23.6	11.9
Group without conversion						
Series 2, 3 (16 cases)	5.8	2.9	5.0	3.6	3.9	2.8
Group with gram-negative flora prior to chemotherapy						
Series 2, 3 (13 cases)	7.0	3.4	6.0	5.1	4.1	3.2

* See table 3 for explanation.

whom the gram-negative flora became predominant. Excluded were a number of patients who had, in addition to respiratory disease, some underlying defect, such as congenital heart disease, cystic fibrosis of the pancreas or mongolism. Again the "converted" group presented more severe clinical disease and illness of longer duration than the group of "nonconverted" patients.

It cannot be definitely stated that this increased severity of illness (in the converted group) was due, *per se,* to the change in bacterial flora. It is possible that the transition in flora might have occurred merely as a result of a more severe illness with decreased resistance to gram-negative organisms.

In the total group of 90 patients studied there were five deaths. These occurred in children who had "converted" to a gram-negative flora or who had an original and persisting gram-negative flora in the throat and nasopharynx. All were infants under 2 years of age with pneumonia; in two this complicated congenital cardiac disease and in one it was associated with cystic disease of the pancreas. Postmortem examinations were performed on four of the five fatal cases. In three of these four children, gram-negative bacilli were demonstrated throughout the alveolar exudate. In the fourth child who had only minimal bronchopneumonia complicating congenital heart disease, no microörganisms could be found. These findings indicate that the gram-negative bacillary flora was present not only in the nasopharynx and throat but also had spread into the lung tissue, and are suggestive of the potential pathogenicity of this group of microörganisms when they invade the respiratory tract.

Discussion

It has long been known that the skin and exposed mucous membranes are inhabited by a more or less permanent and characteristic bacterial flora. Many chemotherapeutic agents and antibiotic substances are effective not only against pathogenic microörganisms, but also against bacterial species normally present. This investigation was undertaken to determine whether penicillin used alone or in conjunction with the sulfonamides brings forth a change in the bacterial flora of the nasopharynx and the throat, and whether such a change influences recovery from primary infection. In 68 consecutive cases studied, conversion to a gram-negative bacillary flora occurred following therapy in 30 cases; in 13 additional cases there was an increase in the number of pre-existing gram-negative bacilli. It is possible that this change in the bacterial flora was greatly favored by the presence on the ward of other children harboring such gram-negative bacilli.

Penicillin in the usual therapeutic dosage is effective against the various cocci present in the upper respiratory tract and is rather ineffective against the gram-negative bacilli. It seems possible, therefore, that therapy with penicillin eradicated the organisms responsible for the original infection as well as those cocci making up the normal bacterial flora, and thus may have encouraged the growth of resident or accidentally introduced gram-negative bacilli.

The question naturally arose as to whether the increase in the number of gram-negative bacilli or their appearance influenced the clinical course of the disease. The analysis of the foregoing data strongly indicates that the "converted" patients harboring large numbers of gram-negative bacilli in the upper respiratory tract had an illness which was more severe and of longer duration than the control group. Moreover, in three of four children in whom autopsy was performed pneumonia was found and gram-negative bacilli were dem-

onstrated in the lung tissue. It seems likely, therefore, that these microörganisms represented at least a contributing factor in the development of the pulmonary disease. Since 9 of 10 patients given penicillin by aerosol inhalation converted to a flora predominant with gram-negative bacilli it would seem that this mode of administration is more likely to produce conversion than when penicillin is given by other routes alone.

It seems logical that in the treatment of severe coccal infections in infants (hospitalized) penicillin should be combined with some other chemotherapeutic or antibiotic agent in order to control the growth of gram-negative bacilli. Probably aureomycin and chloromycetin may fill this need; the effect of sulfadiazine was not striking.

Summary

A study was carried out on 90 children to determine whether conversion to a gram-negative bacillary flora of the nasopharynx and throat takes place during therapy with penicillin, either alone or in conjunction with sulfonamides, and to evaluate the influence of such a conversion on the course of the infection.

Following the demonstration of "conversion" in 22 selected cases, a change to a gram-negative bacillary flora was observed in an additional 30 out of 68 unselected children. The gram-negative bacilli encountered in this conversion group included members of the E. coli-A. aerogenes group, Ps. aeruginosa, A. fecalis and K. pneumoniae; these organisms became predominant in 23 out of the 30 cases of the unselected group. In 22 cases in this latter group the gram-negative bacillary flora was present prior to commencement of specific therapy; however, there was an increase in the number of these organisms in 13 instances. Conversion did not take place in 16 cases.

Vomiting *per se* was not responsible for the conversion since it occurred more frequently in the nonconverted group and vomiting was not a prominent feature of the converted patients.

Of 10 patients receiving penicillin as "aerosol," nine converted to a predominantly gram-negative bacillary flora.

The administration of sulfonamides in conjunction with penicillin did not materially lower the incidence of conversion.

Clinical evaluation of the patients showed that, on the average, the children who had "converted" had a more severe illness and one of longer duration than those of the nonconverted group.

Five patients of this group, all under 2 years of age, succumbed. Autopsy was performed in four and revealed the presence of gram-negative bacilli in the lung tissue of three of them.

The significance of these data is discussed.

Acknowledgment

The authors wish to express their thanks to Miss Dessie W. Will for her technical assistance.

References

1. Lipman, M. O., Coss, J. A., and Boots, R. H., Changes in bacterial flora of throat and intestinal tract during prolonged oral administration of penicillin, J. Bact. **51**:594, 1946.
2. Castex, Capdehourat and Rechniewski, quoted in letter to American Medical Association, J.A.M.A. **138**:308, 1948.

3. Weinstein, L., Spontaneous occurrence of new bacterial infections during course of treatment with streptomycin or penicillin, Am. J. M. Sc. **214**:56, 1947.
4. Stanley, M. M., Bacillus pyocyaneus infections, Am. J. Med. **2**:253 and 347, 1947.
5. Appelbaum, E., and Leff, W. A., Occurrence of superinfections during antibiotic therapy, J.A.M.A. **138**:119, 1948.
6. Sommer, L. S., and Favour, C. B., Biologic complications of penicillin therapy, Am. J. Med. **7**:4 and 511, 1949.
7. Foley, G. E., and Winter, W. D., Increased mortality following penicillin therapy of chick embryos infected with candida albicans, var. stellatoidea, presented at the 49th General Meeting, Society of American Bacteriologists, Cincinnati, May 1949.

SPANISH ABSTRACT

Penicillina y sus Effectos en la Produccion de una Flora Bacilar Gram-Negativa en el Aparato Superior Respiratorio de Niños

Un estudio fue realizado en 90 niños para determinar si la conversión de la flora Gram-negativa de la nasofaringe y de la garganta toma lugar durante el uso de la penicilina sola o combinada con sulfas y para determinar si esa "conversion bacteriana" influye algo en el curso de la infeccion. Esta "conversion bacteriana" fue demonstrada en 22 casos seleccionados asi como en 30 casos de 68 unseleccionados. La flora Gram-negativa encontrada en el grupo de "conversion" incluye miembros del grupo E. coli—A. aerogenes, Ps. aeruginosa, A. fecalis, K. pneumonia; estos organismos fueron prominentes en 23 de los 30 casos estudiados. En 22 casos la flora Gram-negativa estuvo presente antes del comienzo del tratamiento sin embargo el numero de estos organismos aumento en 13 occasiones. Esta "conversion" bacteriana no occurio en 16 casos tratados. El vomito per se no fue la causa de esta conversion ya que occurio mas frequentamente en el grupo de casos en que esta "conversion" no occurio. De 10 pacientes que recibian penicilina "aerosol" 9 fueron convertidos a una flora de bacillos gram-negativo. La administracion simultanea de penicillina y sulfas no disminuyó la incidencia de conversion.

La evaluacion clinica de los patientes demonstró que la majoria casos que obtuvieron "conversion bacteriana" sufrieron una enfermedad mas severa y prolongada que el grupo de pacientes sin "conversion bacteriana."

Cinco pacientes del grupo que experimento "conversion bacteriana" fallecieron todos menores de dos años de edad. La autopsia en cuatro casos demonstró la presencia de bacillos gram-negativo en los pulmones en tres casos. Los autores consideran estos hallazgos como indicativos de la virulencia potencial de este grupo de microorganismos cuando aparecen en el aparato respiratorio.

3144 Jefferson Avenue, Cincinnati

PERNICIOUS ANEMIA IN AN EIGHT YEAR OLD GIRL

Additional Observations in a Case Previously Reported as "Nutritional Anemia in an Infant Responding to Purified Liver Extract"

By LEONARD ROSENZWEIG, M.D., AND LIEUT. COL. OGDEN C. BRUTON, M.C., U.S.A.
Baltimore

PERNICIOUS anemia in childhood is extremely rare. Macrocytic anemias in infancy are not uncommon. Many of these are found to be associated with a megaloblastic pattern in the bone marrow, and in some cases an associated achlorhydria is observed. Folic acid and liver therapy are effective in the treatment of these anemias. Zuelzer[1] reported 25 cases of anemia associated with a megaloblastic bone marrow. Bachman[2] and Peterson and Dunn[3] reviewed the literature dealing with macrocytic and "pernicious" anemias of infants and children and reported that the findings in the peripheral blood and bone marrow resembled closely the findings in the blood and bone marrow of adults with pernicious anemia; however, the associated clinical findings and the course of these cases under treatment showed marked differences. In general, the pernicious-like anemias in infancy and childhood appear to be acute and temporary rather than chronic; and after an initial course of therapy with either liver or folic acid, the blood picture is restored to normal and no further treatment is necessary. The associated achlorhydria, likewise, is not persistent. The occurrence of true addisonian pernicious anemia in childhood is doubted by some authorities.[4,5] Peterson and Dunn[3] considered that the diagnosis of pernicious anemia was justified if the following criteria could be satisfied:

1. Macrocytic anemia
2. Achlorhydria resistant to histamine
3. Megaloblastic bone marrow
4. Specific response to liver as indicated by reticulocytosis following liver and conversion of bone marrow to normoblastic pattern
5. Necessity of continuous therapy to maintain a continuous remission; i.e., relapse upon withdrawal of specific therapy

To these criteria, another might be added, namely, that other causes of macrocytic or megaloblastic anemia be excluded. Up to 1946, Peterson and Dunn were able to find only three cases, including one of their own, which fulfilled the preceding criteria. The case of Benjamin[6] has since been reported.

Fouts and Garber[7] reported a case study of a 4 month old female infant with a severe anemia refractory to the administration of iron, brewer's yeast and other vitamin B preparations. Blood transfusions were of only temporary benefit. Studies of the peripheral blood showed anisocytosis and some macrocytosis, but no hypochromia. The authors felt that this was a nutritional anemia, the fetus having received only minimal amounts of antianemic factor due to a protein-deficient diet of the mother during her pregnancy. The administration of purified liver extract (reticulogen®) was followed by a prompt reticulocytosis (26.8%) and a rise in red blood cells and hemoglobin to normal values. There

From the Pediatric Section, Medical Service, Walter Reed General Hospital, Washington, D. C.
(Received for publication Dec. 8, 1949.)

was also marked improvement in the general condition of the infant. The weight gain, which had totaled only 200 gm. during the four months preceding liver therapy, totaled 3125 gm. during the 4 months following the institution of such therapy. A normal amount of free hydrochloric acid was reported following the administration of histamine. Following discharge from the hospital, the child continued to receive reticulogen® at more or less regular intervals until the age of 8 years.

In the light of subsequent study this case, originally reported by Fouts and Garber[7]

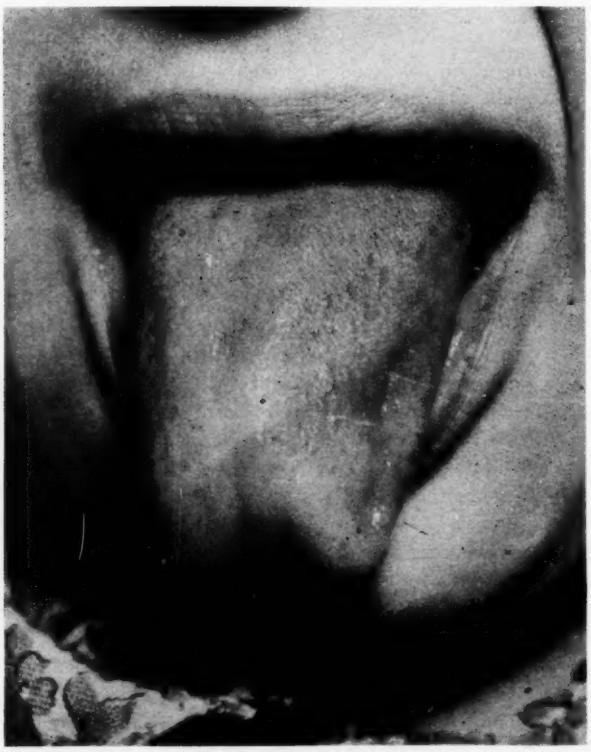

FIG. 1. Appearance of tongue before folic acid therapy showing papillary atrophy.

as "Nutritional Anemia in an Infant Responding to Purified Liver Extract," has now been found to satisfy the criteria established by Peterson and Dunn and may consequently be considered as an additional case of pernicious anemia in childhood. The demonstration of the absence of intrinsic factor in the gastric juice would be conclusive proof. To the authors' knowledge, this has only been performed in children in two instances.[6,8] Because of the extreme rarity and the unusual interest of this clinical picture in childhood, this progress report of the case is presented.

PROGRESS REPORT

S. D., an 8 yr. old white female, was first seen in the Pediatric Out-Patient Clinic of the Walter Reed General Hospital in Jan. 1949. The child had been receiving liver extract therapy since infancy and

blood studies had remained normal or near normal. When first seen at Walter Reed, RBC count was 4.35 million; Hgb., 13 gm./cmm.; WBC count, 9.9 thousand, with 61% neutrophils, 28% lymphocytes and 1% eosinophils. Reticulocytes were .17%. At this time liver injections were temporarily discontinued to determine whether the liver extract was still necessary for the maintenance of normal blood values. Blood values remained essentially unchanged for 2 months, when a definite drop was first noted. Values for RBC and Hgb. fell, and associated with this there developed a moderate leukopenia with a relative lymphocytosis. Two weeks after the development of the anemia, the child was admitted to the hospital for further study. The family history did not reveal any similar ailment. The patient had survived the usual childhood diseases, including pneumonia, without complications. Diet and vitamin intake had been adequate, eggs and certain vegetables being the only foods consistently refused. Weight gain and growth had been steadily upward. No gastrointestinal disturbances had been noted, and the child tended to be constipated.

Physical examination: Patient was of slight build but normal proportions. Height was 115 cm. and weight 20.9 kg. Mucous membranes were quite pale, and there was definite atrophy of papillae of the tongue, most marked anteriorly and along the lateral margins (Fig. 1). Lymph nodes were not enlarged, and spleen was barely palpable. Liver was felt at one fingerbreadth below costal margin. Examination of CNS revealed no abnormalities; vibratory sense was intact.

Laboratory Studies

I. Hemogram

A. Peripheral

1. RBC count: 2.63 million; WBC count, 3.1 thousand; neutrophils, 29%; lymphocytes, 56%; monocytes, 2%; eosinophils, 4%; Hgb., 7.9 gm./100 cc.; hematocrit, 26; reticulocytes, 0.5%; platelets, 570,000 (normal, 500,000-1,000,000); mean corpuscular volume, 99; mean corpuscular Hgb., 30; mean corpuscular hemoglobin concentration, 30; Lee-White clotting time, 8 min.; much variation in red cell size with many large cells well filled with Hgb.; also, many small cells with more small and normal-sized cells than large cells.

TABLE 1

Bone Marrow Studies Showing Differential in Per Cent: (1) During Relapse; (2) 8 Days After Folic Acid Therapy; (3) During 2nd Relapse; (4) 8 Days After Vitamin B_{12} Therapy

	(1) Before Therapy 1st Relapse	(2) 8 Days After Folic Acid Therapy	(3) Before Therapy 2nd Relapse	(4) 8 Days After Vitamin B_{12} Therapy
Blasts	0.8	0	0	0
Undifferentiated myelocytes	6.4	5.0	3	1
Differentiated myelocytes	7.6	1.3	3	6
Metamyelocytes	11.4	9.3	26	25
Adult granulocytes	9.6	22.6	18	20
Bizarre granulocytes	3.0	.1	0	0
Lymphocytes	16.4	14.3	18	11
Proerythroblasts	4.0	2.3	2	0
Basophilic normoblasts	17.6	7.3	10	2
Polychromatophilic normoblasts	4.8	34.6	7	27
Orthochromatic normoblasts	1.0	2.0	3	6
Basophilic megaloblasts	12.8	0	8	0
Polychromatophilic megaloblasts	3.6	0	1	0
Orthochromatic megaloblasts	0.2	0	0	0
Mitotic figures	0.8	0	1	0
Plasma cell	0	0	0	1
Reticulum cell	0	0	0	1

2. Fragility Test: Beginning hemolysis: patient, .48%; control, .44%. Complete hemolysis: patient, .32%; control, .32%.

B. Bone Marrow[9, 10] (table 1)

Before therapy, marrow obtained from iliac crest was typically megaloblastic and predominant cells of the red series were young basophilic normoblasts and basophilic megaloblasts.*

II. Gastrointestinal System

A. Normal small intestine and normal large bowel by barium contrast studies.

B. Stools revealed no occult blood, ova or parasites.

C. Stool fat, 25.2 and 30.8 gm./100 gm. dried weight. Diet included normal amounts of fat.

D. Achlorhydria, refractory to histamine (0.5 mg.),[11] found before and after start of folic acid therapy.

III. Liver Function

A. Complete excretion of 2.0 mg./kg. bromsulfalein in 45 min.

B. Thymol turbidity, 2 u.

C. Cholesterol, 110 mg./100 cc. blood; cholesterol esters, 79 mg./100 cc.

D. Total protein, 6.4 gm./100 cc. blood; albumin, 4.3; globulin, 2.1, A/G ratio, 2.

E. Prothrombin time, 14 sec.; control, 13 sec.

IV. Kidney Function

A. Albumin in small amounts was found occasionally in the urine and was apparently not orthostatic. No impairment of renal function was demonstrated. The child concentrated urine to a specific gravity of 1.028 and had a blood urea nitrogen of 9 mg./100 cc.

V. Bile Pigments

A. Icteric index, 8.

B. Van den Bergh, 0.4 mg. direct; 0.9 mg. indirect.

C. 24 hr. urobilinogen excretion (urinary), 1.25 to 2.5 mg.

VI. Miscellaneous

A. Cardiolipin microflocculation, negative.

Course in Hospital

Treatment was deferred for 12 days while the studies just presented were being performed. The patient was fed the routine ward diet for children of her age, and this was well taken without any intolerance or gastrointestinal symptoms being noted. During the study period many reticulocyte counts were made and in all instances were found to be less than 1%.

Since it was known that the patient had responded previously to purified liver extract therapy and presumably would also respond to vitamin B_{12}, it was decided that the response to folic acid[12, 13] would be tested for a short trial period first. A blood count at this time showed the following: RBC count, 2.42 million; WBC count, 6.65 thousand; Hgb., 7.2 gm./100 cc.; neutrophils, 11%; lymphocytes, 88%; eosinophils, 1%; hematocrit, 24; reticulocytes, 0.8%; platelets, 570,000; MCV, 99.6; MCH, 29.7; MCHC, 30.

Folic acid, 15 mg. daily by mouth, was then started. Three days later the reticulocyte count was 4.1%, and a peak of 17.9% was reached on the 5th day of therapy. The reticulocytes gradually fell to normal limits by the 20th day.[14] Accompanying the reticulocytosis there was a progressive rise in RBC count and a progressive increase in Hgb. and hematocrit (chart 1). A bone marrow study on the 8th day after the start of therapy, when the reticulocyte count was 9.7%, showed a complete disappearance of megaloblastic cells (table 1). There was a normoblastic hyperplasia, with the predominant red cell being the polychromatophilic normoblast. In the pretreatment marrow the predominant red cell had been the basophilic normoblast and the basophilic megaloblast. Folic acid therapy was discontinued after 24 days, at which time the atrophy of the papillae of the tongue was no longer noticeable (Fig. 2) and no neurologic changes had developed. At the conclusion of therapy RBC count had reached 3.99 million, Hgb. 10.1 gm./100 cc., hematocrit 36. WBC count was 4.65 thousand with 51% neutrophils and 46% lymphocytes.

* The Wright stained smears of the bone marrow in this case were examined by Dr. Russell Haden, Dr. Jack J. Rheingold and Dr. C. Lockard Conley, who were all of the opinion that this was a megaloblastic marrow identical with that seen in adults with pernicious anemia.

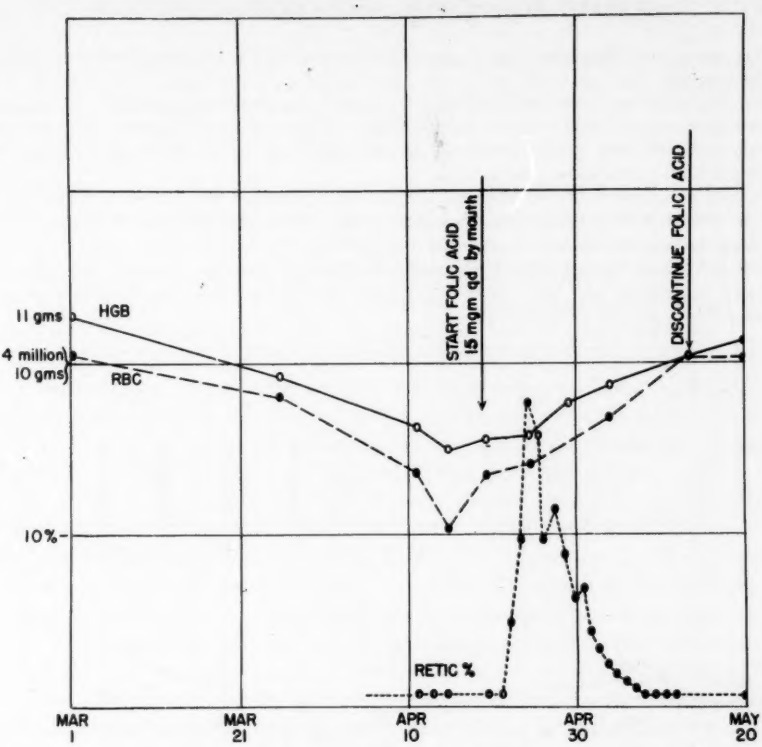

CHART 1. Response of red blood cells, hemoglobin and reticulocytes to folic acid therapy.

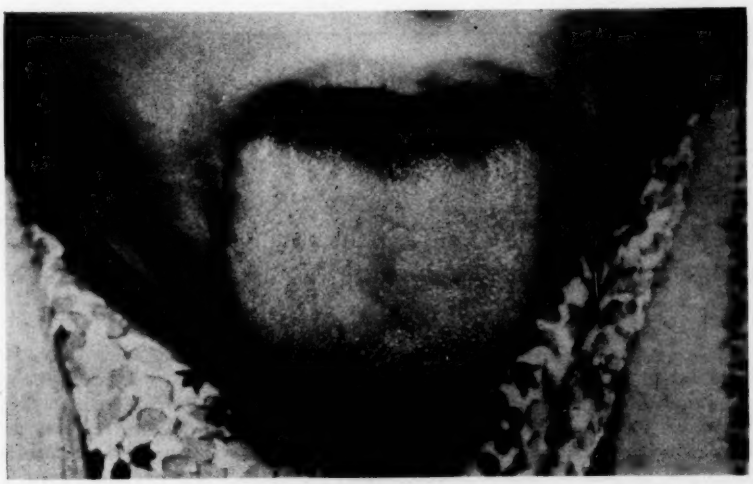

FIG. 2. Appearance of tongue following 23 days' folic acid therapy of 15 mg. daily. Papillary atrophy no longer evident.

The patient was discharged after 4 mo. to be followed in the Pediatric Out-Patient Clinic at weekly intervals.

Her hemogram was essentially unchanged 3 mo. later. She was not seen again for 3 wk., when her hemogram showed RBC count 2.3 million; Hgb., 7.9 gm./100 cc.; hematocrit, 29; WBC count, 3.7 thousand, with 84% lymphocytes and 16% neutrophils; MCV, 100; MCH, 31.2; MCHC, 31.2; platelets, 540,000; reticulocytes, 0.1%.

She was readmitted to the hospital and her physical examination was essentially as described on previous admission with marked pallor, smooth tongue which was quite red at margins, normal neurologic findings and absence of other abnormal findings.

Other laboratory findings, second admission: Achlorhydria was again demonstrated, which was refractory to histamine (0.5 mg.). Stool total fat, 14.2 gm./100 gm. dry feces. Bone marrow before and after therapy as recorded in table 1.

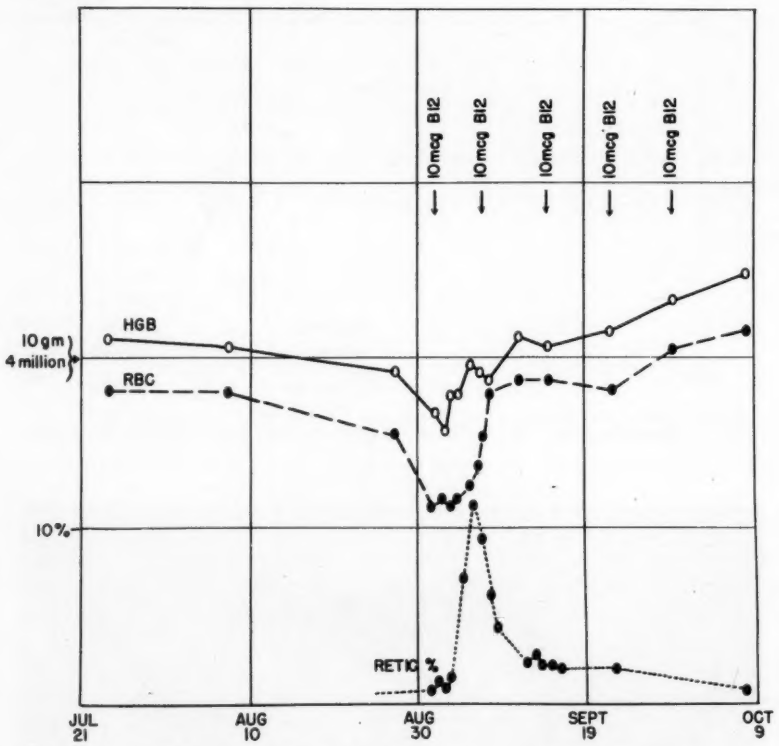

CHART 2. Response of red blood cells, hemoglobin and reticulocytes to vitamin B_{12} therapy.

COURSE IN HOSPITAL, SECOND ADMISSION

Since the patient had been studied completely on her previous admission, only the studies just mentioned delayed her therapy. It was decided to treat her with vitamin B_{12} and 3 days after admission she was given vitamin B_{12} 10 μg, which was repeated at weekly intervals. A similar response to that observed when given folic acid, i.e., reticulocytosis, increase in RBC and Hgb. may be seen on chart 2. Within 48 hr. after first injection of vitamin B_{12} there was apparent less redness of the tongue margins, the patient appeared in better spirits, and the mother spontaneously remarked on the patient's improved personality and sense of well-being. A bone marrow study was done on the 8th day after start of therapy and showed essentially the same changes as on previous admission with

folic acid treatment. Differential of bone marrow may be seen in table 1. Sixteen days after treatment was started RBC count showed 3.65 million and Hgb. 10.2 gm./100 cc. She was discharged from the hospital to be followed in the Pediatric Out-Patient Clinic.

Discussion

It is felt that the course of this 8 year old patient fulfills all the criteria to justify the diagnosis of pernicious anemia: macrocytic anemia, achlorhydria resistant to histamine, megaloblastic bone marrow, reticulocytosis and conversion of bone marrow to normoblastic marrow following specific therapy, relapse on withdrawal of specific therapy, and exclusion of other causes of macrocytic anemia. As far as can be determined, there are no significant differences in this case and pernicious anemia as seen in adults.

It is interesting that during the early course of treatment with both folic acid and vitamin B_{12} there appeared a lag in the increase in hemoglobin as evidenced by the diminished color index. This hypochromic state was even more evident in the stained smear of peripheral red blood cells. Since this development of hypochromia presumably represents the depletion of the patient's previously abundant iron store, she was given iron in the form of ferrous sulfate. This modified picture in macrocytic anemia due to a coexistent iron deficiency has been observed[3] in other stages of this disease in children.

Although the exact dosage of vitamin B_{12} required for patients over a long period of time is unknown and the protective action of vitamin B_{12} against the development of combined system disease over a long period is also undetermined, at the present time it appears that this substance will prove to be satisfactory for the treatment of pernicious anemia. It has been chosen for continued therapy in this patient because there is no evidence to date that it will not prove a satisfactory substance, and the patient prefers it to liver extract, having experienced mild reactive symptoms in the past to liver extract, as well as more pain at the site of injection with liver extract than with vitamin B_{12}.

Summary

A progress report on an 8 year old female diagnosed as "nutritional anemia" at 4 months of age is presented.

The patient's good response, both clinically and hematologically, to folic acid and vitamin B_{12} during relapse has been observed.

She now appears to fulfill all criteria for the diagnosis of pernicious anemia and because of its rare occurrence in childhood she is reported as an additional case of that disease.

Acknowledgment

The authors gratefully acknowledge the assistance of Miss Doris Yoder, for the studies of the peripheral blood, and Captain Julius Krevans, M.C., A.U.S., who assisted in the study of the bone marrow.

References

1. Zuelzer, W., Megaloblastic anemia in infancy, Am. J. Dis. Child. **71**:211, 1946.
2. Bachman, A. L., Macrocytic hyperchromic anemia in early infancy: Report of case and review of literature, Am. J. Dis. Child. **52**:633, 1936.
3. Peterson, J. C., and Dunn, S. C., Pernicious anemia in childhood, Am. J. Dis. Child. **71**:252, 1946.
4. Holt, L. E., and Howland, J., Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1939.
5. Cooley, T. B., and Lee, P., Pernicious blood pictures in infancy, J. Pediat. **1**:184, 1932.

6. Benjamin, B., Infantile form of pernicious (Addisonian) anemia, Am. J. Dis. Child. **75**:143, 1948.
7. Fouts, P. J., and Garber, E., Nutritional anemia in infant responding to purified liver extract, Am. J. Dis. Child. **64**:270, 1942.
8. Pohl, C., Ueber Perniziöse Anämie im Kindesalter, Monatschr. f. Kinderh. **84**:192, 1940.
9. Jones, O. P., Morphologic, physiologic, chemical and biologic distinction of megaloblasts, Arch. Path. **35**:752, 1943.
10. Dameshek, W., and Valentine, E., Sternal marrow in pernicious anemia, Arch. Path. **23**:159, 1937.
11. Wolman, I. J., Gastric digestive secretions in infancy and childhood, Am. J. M. Sc. **206**:270, 1943.
12. Spies, T. D., et al., Further observations of specificity of folic acid molecule, George R. Minot Symposium on Hematology, edited by W. Dameshek and F. H. L. Taylor, New York, Grune & Stratton, 1949.
13. Peterson, J. C., Pernicious anemia in infants and children: Response to folic acid, Am. J. Dis. Child. **73**:578, 1947.
14. Minot, G. R., and Castle, W. B., Interpretation of reticulocyte reactions, Lancet **3**:319, 1935.

SPANISH ABSTRACT

Anemia Perniciosa en Una Niña de Ocho Años de Edad. Observaciones Addicionales Sobre un Caso Previamente Reportado Como "Anemia Nutricional" con Repuesta Favorable al Extracto Purificado de Higado

Se presentan notas adicionales en una niña de ocho años de edad que a los cuatro meses de nacida fué diagnosticada como "anemia Nutricional." El paciente demostró lo siguiente: Anemia macrocitica con medula osea de tipo megaloblastico, achlordia resistente a la histamina y atrofia papilar de la lengua. No se observaron signos o sintomas neurologicos.

El tratamiento con acido folico resultó en una rapida repuesta reticular con remission de la anemia y conversion de la medula osea a un tipo normoblastico. La suspension del tratamiento con el acido folico resultó en una recurrencia de la enfermedad, la cual respondió otra vez favorablemente con el uso de la vitamina B_{12}. Los autores estiman que a pesar de la rara incidencia de anemia perniciosa en niños, el caso reportado llena los caracteres necessarios para su diagnostico.

The Johns Hopkins Hospital

ELECTROENCEPHALOGRAPHIC FINDINGS IN SICKLE CELL ANEMIA

By FONTAINE S. HILL, M.D., JAMES G. HUGHES, M.D., AND BILLIE CAMP DAVIS, B.S.
Memphis

WHILE the central nervous system manifestations in sickle cell anemia have been described by several observers,[1-7] no previous reports on the electroencephalographic findings in this disease have been found. It is the purpose of this paper to present an analysis of the electroencephalograms (EEG) of 38 patients with sickle cell anemia, two of whom were adults. In addition, evidence is presented to correlate the nature of the brain potentials with the clinical manifestations in these cases, as well as with published observations on pathology of the central nervous system.

Although the term sickle cell crisis is becoming less acceptable, it is employed to indicate an exacerbation of symptomatology due to the underlying process. Eight of the 38 patients studied were in a state of sickle cell crisis. The rest of the subjects were brought to the hospital as ambulatory patients. The history and physical findings were reviewed, with special reference to the nervous system. An EEG, electrocardiogram (ECG), roentgenologic survey of chest and bones, and a detailed neurologic examination were obtained on each patient. The diagnosis of sickle cell anemia was established in each case before it was included in the series. The usual criteria were employed, and all doubtful cases were excluded.

While it is not the authors' intent to review fully the manifestations shown by the central nervous system, brief mention of them will give a clearer background for an understanding of the electroencephalographic findings. All who have written on the involvement of the nervous system in sickle cell anemia have emphasized the variability of the clinical picture. The general condition of the patient may be one of drowsiness, stupor, delirium or convulsions. Irritability and headaches are common, and even psychotic episodes have been noted. There may be disturbances of sight, speech and hearing. There may be weakness or paralysis of extremities, or of muscles innervated by the cranial nerves. Severe pain in almost any part of the body may be present, but it is generally worse in the abdomen and in the extremities. The neck and back may be stiff and painful. Variable disturbances of reflexes are noted. The spinal fluid findings range from normal to grossly bloody and abnormal.[1] Death may occur during episodes accompanied by involvement of the nervous system, the patient may recover fully, or there may be permanent residual neurologic damage.

Although there have been many interpretations of the pathologic picture in the brain,[1,2,6,7] it is generally acknowledged that blocking of blood vessels is the dominant factor. This interference with blood supply to various portions of the brain is accom-

From the Pediatric Division, College of Medicine, University of Tennessee, and the John Gaston Hospital, Memphis.

Supported by a grant from the United States Public Health Service.
(Received for publication Dec. 3, 1949.)

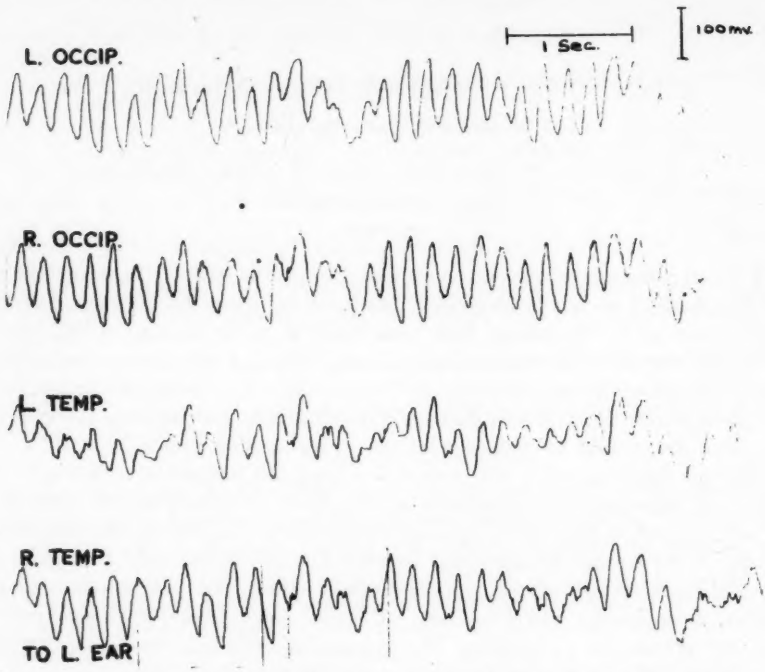

FIG. 1. Abnormal EEG using scalp-to-ear leads on 2 yr. old male who had no symptoms referable to CNS.

panied by changes in the nerve cells which vary from slight alterations to complete destruction and replacement by glial fibrosis. Focal lesions, gross and microscopic hemorrhages, and widespread atrophy, especially of the cortex, may occur. It would be strange indeed if these extensive changes in the brains of some of the patients with sickle cell anemia did not result in abnormal EEGs.

METHODS EMPLOYED

EEGs were obtained under standard conditions to assure valid tracings. The machine used was an Offner Type C 144 four channel crystograph electroencephalograph. No sedative agents were used. Eight scalp electrodes were used as follows: 2 frontal, 2 precentral, 2 occipital and 2 temporal. Electrodes were attached to each ear to be used as reference points. Separate scalp-to-ear runs were made from each of the 8 scalp electrodes to the L ear reference electrode. Similar scalp-to-ear runs were made from the 8 scalp electrodes to the right ear reference electrode. In a few cases, scalp-to-ear runs were made using the inter-connected ear electrodes as a reference point. Initial scalp-to-scalp runs were made as follows: L frontal-to-L precentral, R frontal-to-R precentral, L precentral-to-L occipital, R precentral-to-R occipital. The second set of scalp-to-scalp runs were as follows: L frontal-to-L precental, L precentral-to-L occipital, R frontal-to-R precentral, R precentral-to-R occipital. Triangulation technics were employed on both sides as follows: frontal-to-precentral, precentral-to-occipital, occipital-to-temporal, temporal-to-frontal. Whenever an abnormality was noted in a particular area, more sensitive triangulation technics were employed to localize more sharply the site of the abnormality.

EEGs were interpreted according to the Davis system.[8] In addition, alpha index was interpreted according to the scales set up by Lindsley[9, 10] and Bernhard and Skoglund[11] for children of various

ages. This was done in order to differentiate waves in the slow frequency range commonly considered abnormal from those which are, in reality, normal for children of various age groups.

Results Obtained

Of the 38 patients studied, the EEGs were abnormal in 26 instances. Although the number of patients studied during sickle cell crisis was relatively small, all this group showed abnormal tracings. The great majority who were not in crisis also showed cerebral dysrhythmia.

In general, the most consistent findings were marked irregularity, lack of sustained rhythm, high microvoltage and a high percentage of slow wave activity. One of the most noticeable findings was the occurrence of sharp waves of high microvoltage appearing singly and in bursts throughout the record. Phase reversals, usually of abnormally high microvoltage, appeared in 25 of the 26 abnormal records. These inversions occurred in bursts and as random waves, and they were characterized also by sharp waves or spikes. The EEGs of the two adult patients were remarkably similar, both having a high percentage of fast frequencies, 11 to 30 cycles/sec., and both showing suppression in all leads.

All the scalp-to-ear runs in all the abnormal tracings showed cerebral dysrhythmia. The scalp-to-scalp tracings showed varying degrees of cerebral dysfunction which were most noticeable in the occipital areas.

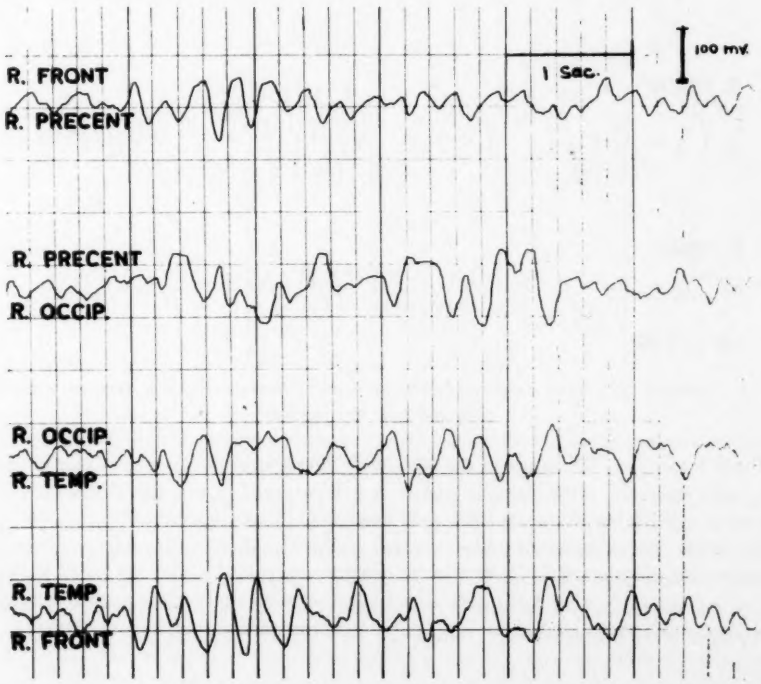

Fig. 2. Abnormal EEG using scalp-to-scalp leads on 9 mo. old female who had symptoms referable to CNS.

Figures 1-5 illustrate the electroencephalographic patterns found in patients with sickle cell disease.

Table 1 relates the age of the patient to the character of the EEG. It is apparent from the table that children under 6 years of age with sickle cell anemia have the highest probability of an abnormal EEG. The likelihood of a normal EEG increases in patients with sickle cell anemia who are 6 years of age or older.

Table 2 indicates the incidence of symptoms possibly referable to the nervous system in the 38 patients studied. It is difficult at times to distinguish symptoms due to nervous system involvement from those due to changes elsewhere.

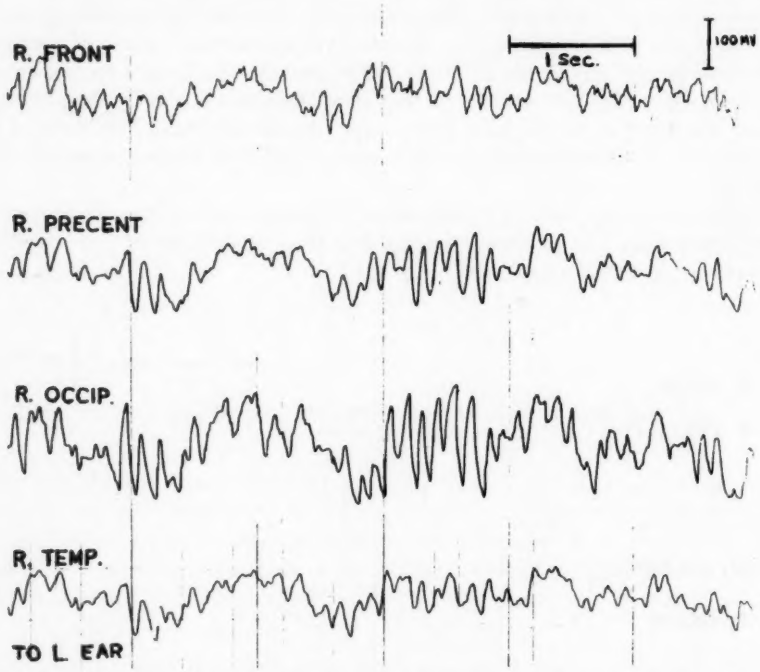

FIG. 3. Abnormal EEG using scalp-to-ear leads on 9 yr. old female who had symptoms referable to CNS and who was in crisis.

Table 3 correlates the nature of the EEG with the presence or absence of past or present symptoms referable to the nervous system. It will be noted that of the 18 children under 6 years of age having abnormal EEG, only five were without central nervous system symptoms. While the incidence of severe nervous system symptoms is not this great, carefully studied patients under 6 years of age do exhibit a high frequency of minor symptoms which are interpreted to be due to involvement of the nervous system. Convulsions, hemiplegia and involvement of comparable severity is the exception, rather than the rule.

The EEGs were abnormal in all eight of the patients studied during sickle cell crisis. Four of these patients were also studied when they were not in crisis. The presence or

absence of crisis did not seem to influence the tracings in these four patients. It may be significant that none of these four children had major nervous system manifestations during their crises.

Hemoglobin determinations were done on 14 patients near the time that the tracings were made. There was no apparent correlation between the severity of the anemia and the presence or absence of abnormal cortical function as determined by the EEG.

Discussion

In view of the widespread nervous system lesions reported by several investigators, there would appear to be ample reason for a high frequency of abnormal EEGs in patients

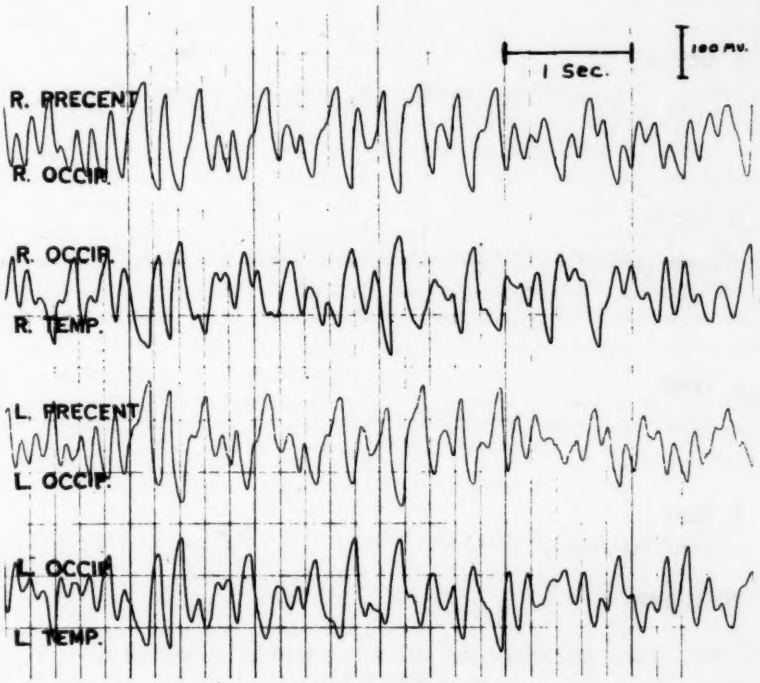

Fig. 4. Abnormal EEG using scalp-to-scalp leads on 5 yr. old female who had symptoms referable to CNS and who was in crisis.

with sickle cell anemia. It is not the purpose of this paper to analyze in detail the various viewpoints which have been expressed in regard to the pathogenesis of the cerebral lesions. In brief, the cerebral changes are thought to be due to blockage of small or large blood vessels which may be on a functional[12] or organic[1] basis.

In regard to organic obstruction of blood vessels, the predominant belief has been that the capillaries of the brain become jammed with sickled erythrocytes, are dilated and congested, and that these changes may be associated with thrombotic lesions in the smaller blood vessels of the brain, the dural sinuses, or the cortical branches of the cerebral artery.

The vascular changes are most noticeable in the cerebral gray matter and in the vessels within the subarachnoid spaces over the hemispheres. Associated changes include infiltrative and degenerative changes in the walls of the blood vessels, perivascular edema, cellular infiltration, hemorrhages and necrosis. Larger arteries and arterioles which supply the cortex may show intimal proliferation, fragmentation and reduplication of the intima, medial fibrosis and hyalinization, and sometimes hemorrhage into the media, with pigmentary changes and calcification. The lumen may be narrowed, and fresh and organized thrombi may be found.

In regard to functional obstruction of blood vessels, Kimmelstiel[12] has recently empha-

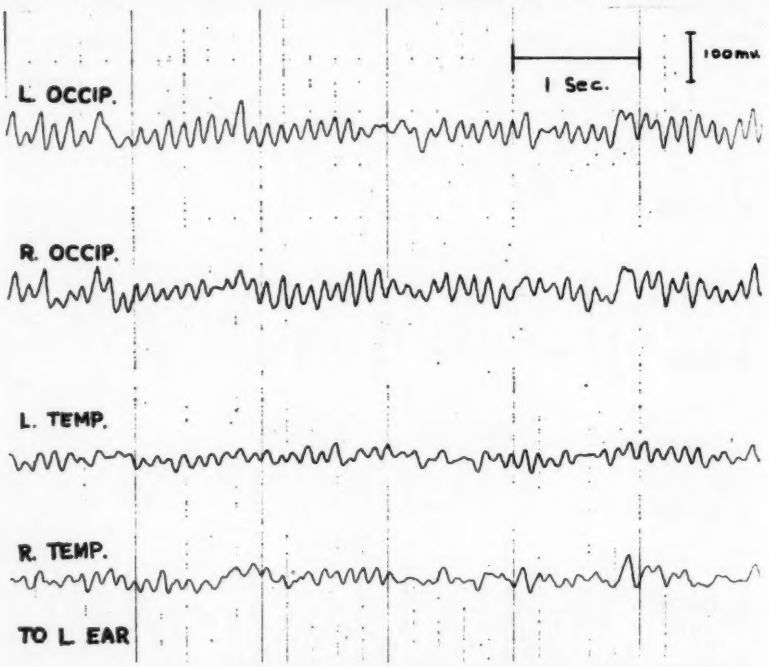

FIG. 5. Normal EEG using scalp-to-ear leads on 6 yr. old female who had symptoms referable to CNS.

sized that in sickle cell disease ischemic infarctions may occur without thrombotic occlusion of arteries. According to his concept, peripheral vascular spasm leads to tissue anoxia and contributes to additional intravascular sickling. The peripheral vascular spasm may lead to capillary dilatation or stasis, or may cause ischemic necrosis. Local ischemia of tissue and capillary walls may result in organic damage to the vessel walls, degenerative changes and thrombosis, resulting in superimposed infarctions. According to this theory, the congestion and packing of capillaries with sickled erythrocytes is the result, rather than the cause, of capillary stasis.

Regardless of whether the functional or organic theory of vascular blockage is correct, or whether they may both be true, there is ample cause for tissue anoxia which should reflect itself in abnormalities of the EEG.

TABLE 1

AGE DISTRIBUTION OF PATIENTS AND CHARACTER OF EEG

Age—Yr.	Normal EEG	Borderline EEG	Abnormal EEG
0–1			6
2–3			5
4–5			7
6–7	3	1	2
8–9	2	2	4
12–13	1		2
14–15	1		
18–19	1		
30–31	1		

While there is much evidence that blockage of blood vessels may be of a permanent nature, it is conceivable that vascular stasis may be so temporary and of such a mild degree that the patient may recover without residual cerebral dysfunction.

Electroencephalography offers a new approach toward determining whether involvement of the nervous system in sickle cell anemia may, at times, be transient and followed by full return of function, not only clinically, but also from the standpoint of electric cortical activity. However, the authors have not yet encountered a patient with nervous system symptoms and an abnormal EEG who has subsequently had a normal EEG. It will require the study of a larger group of patients for a longer period of time in order to establish whether this finding is constant. Many children have been seen with transient nervous system symptoms who have become clinically normal.

It is interesting to note that the three patients 14 years of age or older studied in this

TABLE 2

SYMPTOMS POSSIBLY RELATED TO CNS INVOLVEMENT IN 38 CASES OF SICKLE CELL ANEMIA

Abdominal pain	23
Pain in extremities	18
Headache	16
Drowsiness, stupor or coma	16
Pain in back and neck	13
Irritability	9
Vomiting	9
Pain in joints	7
Paresthesia of extremities	5
Deafness (intermittent)	5
Convulsions	5
Stiffness of neck	2
Priapism	2
Photophobia	2
Incontinence of urine	1
Delirium	1
Diplopia	1
Aphasia	1
Hemiplegia	1
Deafness (complete)	1

series had normal EEGs while all the children under 6 years of age had abnormal tracings. This is no more than suggestive evidence that individuals with sickle cell disease and abnormal EEGs may later have normal brain potentials.

The pathologic findings correlate well with the clinical manifestations. The milder symptoms are probably explainable on the basis of vascular stasis, with or without thrombosis of small blood vessels.Collateral circulation is believed to be good in these cases. The more severe and long lasting symptoms are considered to be due to extensive cerebral damage due to thrombosis of large vessels, or ischemic infarction, in areas where collateral circulation is poor.

Although difficult to prove, individuals with normal EEGs who give definite history of previous nervous system involvement may have passed through a period of temporary vascular stasis without thrombosis, or, if thrombosis and other permanent tissue changes occurred, collateral circulation may have been sufficient to prevent anoxia of the cortex.

TABLE 3

RELATION OF ABNORMAL EEG TO PRESENCE OR ABSENCE OF CNS MANIFESTATIONS AT TIME OF TRACING OR OBTAINED FROM HISTORY

Age—Yr.	Without CNS Symptoms Normal EEG	With CNS Symptoms Normal EEG	Without CNS Symptoms Abnormal EEG	With CNS Symptoms Abnormal EEG
0–1			2	3
2–3			3	3
4–5				7
6–7		4		2
8–9		4		4
12–13		1		2
14–15		1		
18–19		1		
30–31		1		

A proper evaluation of the relationship between electroencephalographic patterns and involvement of the nervous system in sickle cell anemia will have to await study of a larger series of patients over a longer period of time. Correlation of electroencephalographic findings with postmortem examinations is especially necessary.

SUMMARY AND CONCLUSIONS

Electroencephalographic findings in 38 cases of sickle cell anemia are presented, of which 35 patients were children under 14 years of age.

The EEGs were considered to be abnormal in 26 patients. Of special interest was the fact that all children under 6 years of age had abnormal EEGs.

In the group as a whole, there were nine patients with a past history or the presence of nervous system symptoms who had normal EEGs, and three in this group whose tracings were thought to be borderline.

A brief review of the principal pathologic changes in the brain in sickle cell anemia is presented, and a discussion is given of the way in which these changes might influence brain potentials.

Abnormal brain potentials in patients with sickle cell anemia are considered to be due primarily to cerebral anoxia, and secondarily to degenerative processes in nerve cells.

Electroencephalography offers a new approach to the determination of the incidence and character of cerebral dysfunction in sickle cell disease.

ACKNOWLEDGMENT

Dr. L. W. Diggs, Professor of Medicine of the University of Tennessee, and Dr. Hudson Jost, Associate Professor in the Department of Psychiatry of the University of Tennessee and Director of the Psychophysiological Laboratories of Gailor Psychiatric Hospital, gave helpful advice in the preparation of this paper. The authors are also grateful for the technical assistance of Mrs. Glenn Morris Parry in recording many of the electroencephalograms.

REFERENCES

1. Hughes, J. G., Diggs, L. W., and Gillespie, C. E., Involvement of nervous system in sickle cell anemia, J. Pediat. **17**:166, 1940.
2. Wertham, F., Mitchell, N., and Angrist, A., Brain in sickle cell anemia, Arch. Neurol. & Psychiat. **47**:752, 1942.
3. Skoog, A. L., Cerebral complications in sickle cell anemia, South. M. J. **33**:714, 1940.
4. Skoog, A. L., Sickle cell anemia with brain involvements, Dis. Nerv. System **6**:276, 1945.
5. Connell, J. H., Cerebral necrosis in sickle cell disease, J.A.M.A. **118**:893, 1942.
6. Murphy, R. C., and Shapiro, S., Pathology of sickle cell disease, Ann. Int. Med. **23**:376, 1945.
7. Lowe, R. C., and Adams, C. C., Studies on pathophysiology of sickle cell disease, Ann. Int. Med. **22**:192, 1945.
8. Davis, Pauline A., Technique and evaluation of electroencephalogram, J. Neurophysiol. **4**:92, 1941.
9. Lindsley, D. B., Electrical potentials in brain of children and adults, J. Gen. Psychol. **19**:285, 1938.
10. Lindsley, D. B., Longitudinal study of occipital alpha rhythm in normal children: Frequency and amplitude standards, J. Genet. Psychol. **55**:197, 1939.
11. Bernhard, C. G., and Skoglund, C. R., On alpha frequency of human brain potentials as function of age, Skandinav. Arch. f. Physiol. **82**:178, 1939.
12. Kimmelstiel, P., Vascular occlusion and ischemic infarction in sickle cell disease, Am. J. M. Sc. **216**:11, 1948.

SPANISH ABSTRACT

Alteraciones Electroencefalograficas en "Sickle Cell Anemia"

Las alteraciones electroencefalograficas ocuridas en 38 casos de "Sickle Cell Anemia" son presentadas; de los cuales 35 pacientes fueron menores de 14 años de edad. El EEG fué considerado abnormal en 26 pacientes. Todos los niños menores de 6 años de edad demostraron un EEG abnormal.

Del grupo total, 9 pacientes tuvieron historias anterior o sintomas nerviosos, pero en estos casos el EEG fue normal a excepcion de 3 casos que fueron questionables. Se presenta una revision de los principales cambios patologicos en el cerebro en "sickle cell anemia" y de su posible influencia en los cambios de potenciales electricos del cerebro. Estos potenciales electricos abnormales en pacientes con "sickle cell anemia" son considerados primariamente debidos a la anoxia cerebral y secundariamente a procesos degenerativo de las celulas nerviosas.

La EEG ofrece otra forma de estudio para la determinacion de la incidencia y caracter de la disfuncion cerebral en "sickle cell anemia."

20 South Dunlap Street

USE OF DRUGS IN THE DIAGNOSIS AND TREATMENT OF PHEOCHROMOCYTOMA

Case Report

By G. E. McCoy, M.D., and M. L. Bridgeman, M.D.
Muncie, Ind., and Portland, Ore.

HYPERTENSION is a relatively common finding in adults, the most common cause being inherent diseases of the cardiovascular system. The finding of hypertension in a child is unusual and should lead one to use extreme caution before making the diagnosis of essential hypertension. In children, hypertension is almost always secondary to some other disease process, the most common being secondary to some kidney pathology, e.g., acute glomerulonephritis, or unilateral kidney disease (Goldblatt syndrome). Other causes of hypertension in children are: lead poisoning, acrodynia, coarctation of the aorta, hyperthyroidism, Cushing's syndrome, brain tumor involving the hypothalamus, pheochromocytoma and those very few, called essential or idiopathic, in which the cause cannot be established.

Snyder and Vick[1] in 1947 reviewed the literature in special reference to pheochromocytoma in children and reported three additional cases. In their survey of the literature there were only three cases previously reported in children who were known to have clinical hypertension and surgical or pathologic findings present. Since then there have been two other cases in children reported by Cahill[2] and Grimson.[3]*

The usual clinical findings are well known and adequately reported in the literature. These findings will be omitted except as they are brought out in the case presentation. There are two large groups of patients with such tumors: those with paroxysmal hypertension and those in which the hypertension is sustained. The latter type is the most common. In the eight cases previously reported in children, only one showed the classical paroxysmal picture. The case to be presented is one in which the hypertension was sustained.

During the past few years several new drugs have been developed to counteract the effect of the pressor substance which is responsible for the elevated blood pressure in cases with pheochromocytoma. These drugs have been useful agents in helping to establish the cause of hypertension due to the substance or substances released by these chromaffin tumors. Two of the drugs used with varying success are benzodioxain (piperidinomethyl-benzodioxain) and dibenamine® (N, N-dibenzyl-B-chloroethylamine), hereafter referred to as benzodioxain and dibenamine®, respectively. Each has its faults and virtues. At the University of Oregon Medical School the greatest interest has been in regard to the use of dibenamine®.

From the Department of Pediatrics, University of Oregon Medical School, Doernbecher Memorial Hospital for Children, Portland, Ore.

(Received for publication Aug. 15, 1949.)

* Since this paper was submitted, another case has been reported (Litman, N. N., and State, D., Pheochromocytoma, PEDIATRICS 4:735, 1949.)

Histamine,[4] tetra-ethyl ammonium bromide[5] and mecholyl[6] have been used to precipitate bouts of hypertension in patients suspected of having a pheochromocytoma. The use of these drugs is not without danger, because they may elevate the blood pressure to dangerously high levels.

Special radiologic procedures are employed as an aid in localization of a suspected tumor. These consist of intravenous pyelograms, laminograms and perirenal injection of air. Only the first two procedures are without great danger. Should the tumor be elsewhere, e.g., at the organ of Zuckerkandl, these procedures are useless.

All these procedures may or may not be helpful and most of them are not free from considerable danger to the patient. The following case is one of sustained hypertension

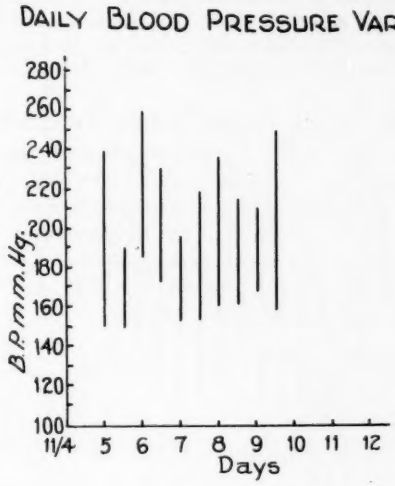

CHART 1

in a child. It will be presented in a step-wise manner representing what would seem to be the most rational method of approach in a patient suspected of having a pheochromocytoma.

CASE REPORT

This 13 yr. old white male was admitted to Doernbecher Hospital because of hypertension, which was discovered following an examination for glasses in which the examiner had noted hypertensive changes in the eye grounds.

The complaint for which the child sought aid was failing vision for the past year. In checking the past medical history more carefully, the child did complain of headaches, episodes of paroxysmal sweating and pain in lumbar area on straining for the past year and a half. The birth, growth and developmental and past medical history were noncontributory.

Physical examination was negative except for hypertension noted in all extremities and hypertensive changes in both eye grounds. Ophthalmologic report: "Anterior segment and vitreous clear. There is marked edema of the nerve heads bilaterally as well as the retina in the posterior poles. There are macular stars and numerous large white exudates and stellate hemorrhages. There is a generalized constriction of the arterial tree as well as marked segmentation. Impression—hypertensive retinopathy—these changes may be reversible." Hypertension was 210/160 and postural hypotension was noted.

Laboratory report: complete blood count and sedimentation rate were normal. Kahn and Kline

tests were negative. Blood type II (A) Rh positive. Urinalysis was normal with good concentration to 1.030 specific gravity; PSP test revealed 55% of the dye excreted in 30 min. and 18% in another 30 min. with a total excretion of 73% in 1 hr. Blood chemistry revealed BUN 10 mg./100 cc. Fasting blood sugar 76 mg./100 cc. Glucose tolerance; fasting blood 78 mg./100 cc.; 45 min. 162 mg./100 cc.; 1 hr. 15 min. 194 mg./100 cc. and 1 hr. 45 min. 143 mg./100 cc. slightly prolonged. Blood sodium and potassium were normal, 346 mg./100 cc. and 19 mg./100 cc., respectively. PPD #1 (tuberculin) was negative. ECG was reported as sinus rhythm with normal tracing.

The following radiologic procedures were made: PA chest—heart and lungs normal.

Flat Plate of Abdomen—psoas shadows normal. No abnormalities noted.

Left lateral and sterio of skull—normal.

Intravenous pyelograms—both pelves are well outlined. There is a moderate indenture on the left pelvis between the superior and middle calyces. Ureters and bladder are normal.

The procedures just described seemed to exclude abnormalities of the kidney, brain, coarctation of aorta, lead poisoning and acrodynia as possible causes. Thus, studies were undertaken to establish variations in blood pressure in response to sedation, cold, posture and the newer blocking agents.

Blood pressures were recorded every 4 hr. and the highest daily pressures are seen in chart 1.

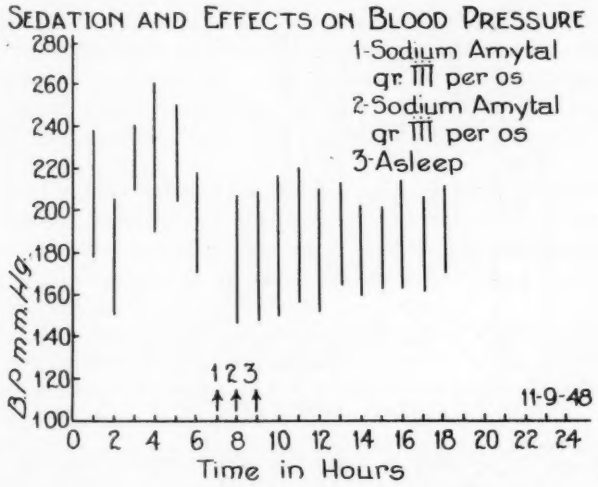

CHART 2

The next procedure was the effect of sedation on blood pressure, shown graphically in chart 2. Sedation did not alter this patient's blood pressure, suggesting that psychogenic factors were not the principal cause of the hypertension.

The lability of the cardiovascular system can also be determined by the cold-posture test as described by Hines and Brown[7-10] and modified by Smithwick.[11] (See chart 3.) There was a marked postural hypotension which is characteristic of pheochromocytomas. The abnormal elevation of pressure in response to ice water is not the usual response in such cases.

It had been proposed by several authors[2, 3, 12] that benzodioxain will cause a reduction in pressure in a patient with a pheochromocytoma and this is well demonstrated in this case by chart 4.

Recently Spear and Griswold[13] have reported the same fall in blood pressure using dibenamine® with the patient in the supine position. This is excellently demonstrated in chart 5. This, according to Gould,[14] is not true if the hypertension is essential or if it is secondary to renal pathology.

It was felt, on the basis of information available at this time, that this patient had a pheochromocytoma, probably of the left adrenal. Likewise it was felt that the use of histamine or mecholyl would not give additional information and might be harmful to the patient. Therefore, the child was scheduled for surgery.

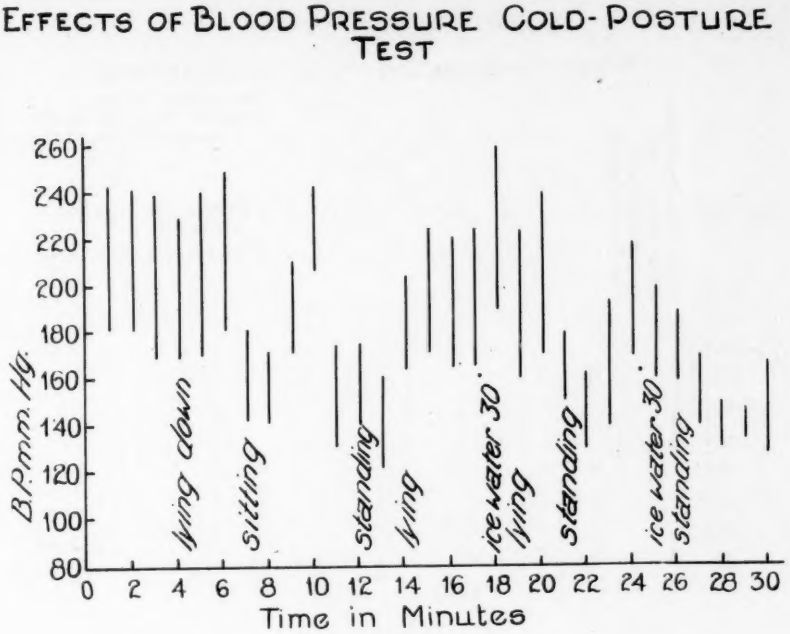

CHART 3

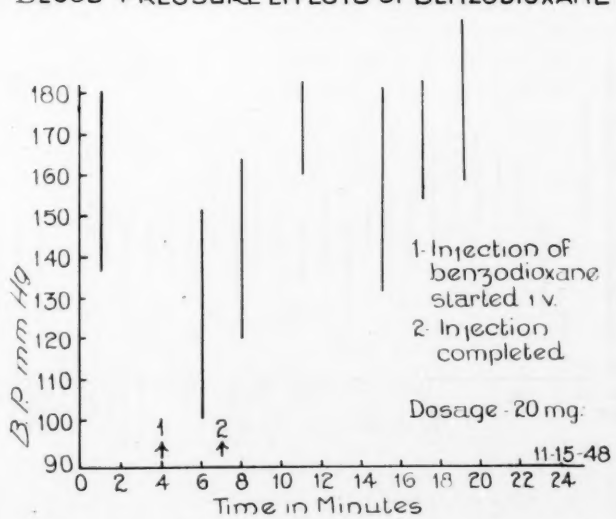

CHART 4

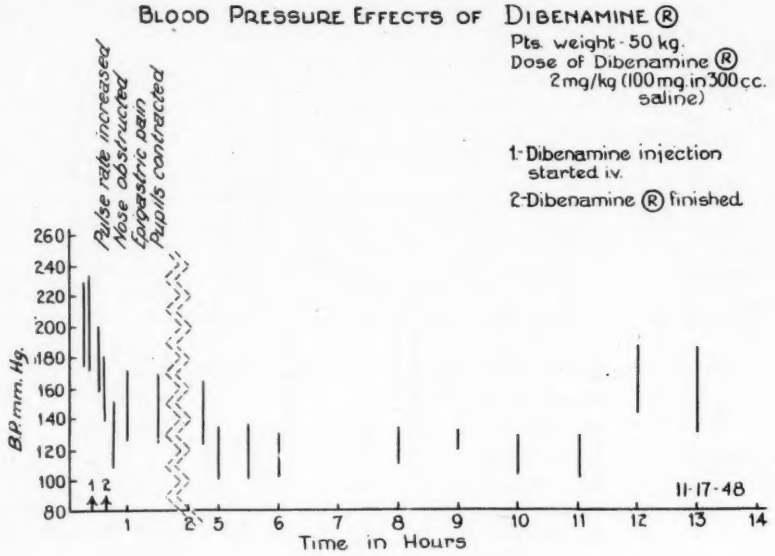

CHART 5

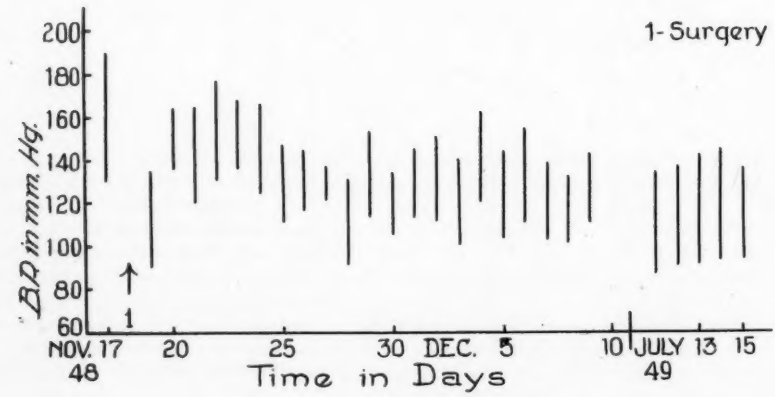

CHART 6

Blood Pressure Effect of Benzodioxane Post-Operatively

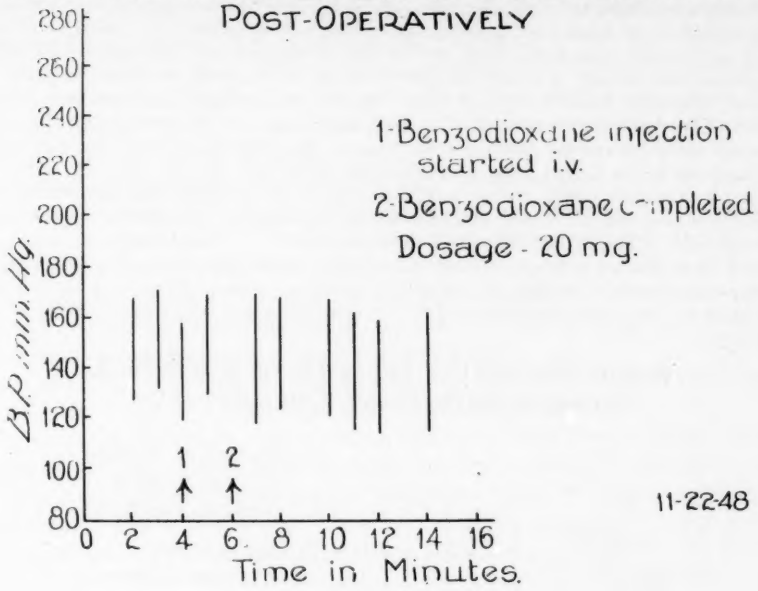

Chart 7

Blood Pressure Effect of Dibenamine ® Post-Operatively

Patients weight - 50 kg.
Dosage-2mg/kg (100 mg. in 300 cc. saline)
1-Dibenamine ® started i.v.
2-Dibenamine ® completed.

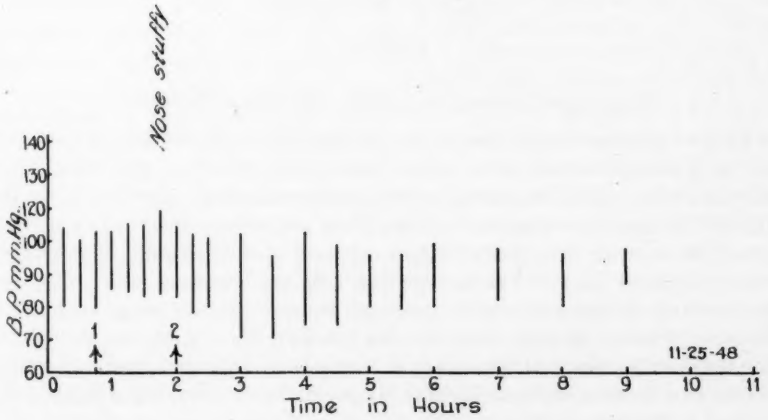

Chart 8

Operation was performed 2 wk. after admission. With avertin induction supplemented with nitrous oxide and ether, an intratracheal catheter was inserted and the patient was maintained on ether. A left paravertebral incision was made, the left 12th rib removed, the diaphragm divided and the left adrenal area exposed. A smooth encapsulated tumor, 4 x 4 cm., of the adrenal was found and removed. The tumor weighed 28 gm. A biopsy was also taken from the perinephric fat and the left kidney. Shortly following the removal of the tumor there was a drop in blood pressure; however, it never fell below 100 systolic. Ambulation was begun on the second postoperative day and the blood pressure began to rise. Chart 6 demonstrates the course of the blood pressure. Since 10% of the cases reported have multiple tumors, another tumor was suspected in this patient. Four days after operation benzodioxain was used and 3 days later dibenamine® was repeated. This time there was no fall in blood pressure. A graphic representation is shown in charts 7 and 8, respectively.

Since there was no response to either benzodioxain or dibenamine®, it was now considered justifiable to determine the effect of histamine. This did not cause an elevation of blood pressure. (See chart 9.) The patient was discharged 21 days following surgery with a blood pressure of about 150/110.

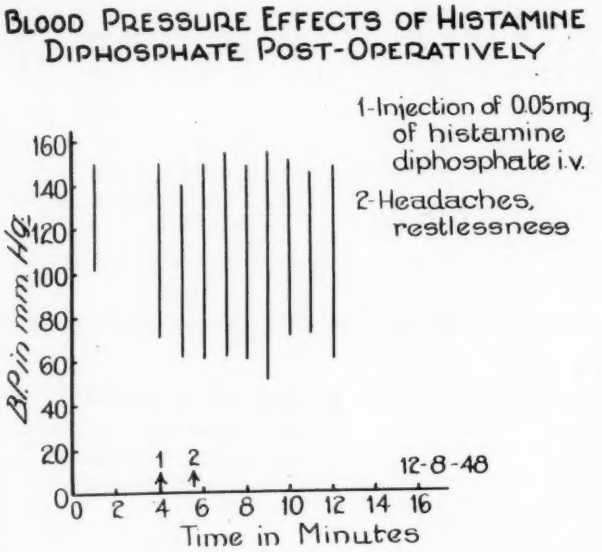

CHART 9

PATHOLOGIC REPORT OF TISSUES REMOVED AT SURGERY

Sections of formalin fixed fragments of the tumor reveal the external surfaces of the tumor to be covered with a rather thick fibrous capsule which in some areas contains within the fibrous tissue remnants of atrophic suprarenal glands. Attached to the outer surface of the capsule are fragments of fatty tissue containing scattered extravasated red cells and blood vessels. The tumor itself is composed of cells arranged in various sized alveolar groupings. The cells for the most part have small vesicular nuclei with a large amount of finely granular acidophilic cytoplasm. In some areas the nuclei are larger and more hyperchromatic. In some areas, they are pyknotic. The cell borders are indistinct, giving the alveolar clusters an appearance of a syncytium. Some multinucleated giant cell forms are seen within a few areas, but this is not considered evidence of malignant transformation in this tumor. Many of the cells show shrinkage and vacuolization of the

cytoplasm and retraction of the alveolar clusters away from the supporting stroma. The supporting stroma is rather abundant although the individual trabeculae are quite narrow; they are quite vascular. Many of the capillaries are dilated and engorged. In some areas there is moderate hemorrhage of recent origin and scattered collections of pigment from older hemorrhage. There are a few small focal collections of lymphocytes. Microscopic examination of the Zenker-fixed tumor tissue with H and E stain reveals much less artifactual shrinkage and degeneration although rather extensive generalized vacuolization is seen. Examination of the perirenal fat reveals a fine, lacy reticulum of a dull adipose tissue with a few small focal areas of recent hemorrhage. Section of kidney reveals a thin capsule and no scarring of the cortex. Glomeruli show no significant changes. Section of one arteriole shows slight thickening of the walls but no hyalinization. Generalized degeneration of the tissue precludes the examination afferent arterioles. Diagnosis: 1. adrenal gland pheochromocytoma, 2. perirenal fat, 3. kidney cortex.

The patient was seen again two months after discharge, at which time his blood pressure was about 140/90. The cold-posture test was normal. (See chart 10.)

The patient was next seen eight months after surgery. Daily blood pressures are seen in chart 11. All the drug tests previously listed were repeated and all were normal (charts 12, 13 and 14). The cold-posture test was also repeated (chart 15). Consultation by the Ophthalmology Department reveals: "There is a remarkable change in the fundus picture. There appears to be marked glial proliferation around both nerve heads. The terminal arterioles appear nearly normal. There are a number of old, deep, choroidal and retinal exudates around the macular area. There are still some segmented areas of retinal constriction. No new exudates or hemorrhages are noted. No retinal edema noted. Impression: This fundus picture is that of a subsided hypertensive retinopathy with no new pathologic processes noted."

Discussion

It has been said that pheochromocytomas are usually histologically benign (only 9% malignant) and physiologically malignant. Certainly this observation is true. These tumors not only elevate the blood pressure to dangerously high levels while present but if this hypertension lasts long enough secondary changes may occur in the vascular tree.

The problem that presents itself in correctly making the diagnosis of pheochromocytoma depends primarily on the nature of the hypertension produced by the tumor. When the hypertension is paroxysmal in type the problem is solved by the use of drugs which will precipitate a rise in blood pressure, e.g., histamine. This response can be blocked by dibenamine®, as reported by Spear and Griswold.[13] This is sufficient evidence to suspect the presence of such a tumor and to justify surgery. On the other hand, sustained hypertension is the type most commonly seen in children associated with a pheochromocytoma. The problem is then one in which the proper selection of drugs will cause a fall in blood pressure thereby indicating the presence of increased circulating epinephrine. Dibenamine® and benzodioxain are such drugs. The only clinically significant hypertension due to the circulating epinephrine which is now known is that associated with a pheochromocytoma. Benzodioxain and dibenamine® have different sites of action, but the net result in the patient is the same. Benzodioxain is an adrenolytic drug which acts by directly blocking the response to epinephrine, but not to adrenergic impulses. Dibenamine®, on the other hand, acts by blocking adrenergic impulses. Will the use of benzodioxain or dibenamine® be dangerous to patients with hypertension from causes other than a pheo-

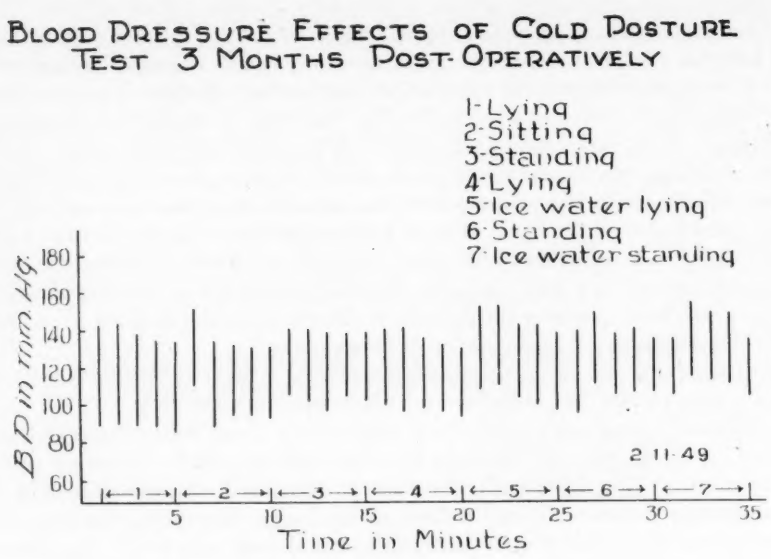

CHART 10

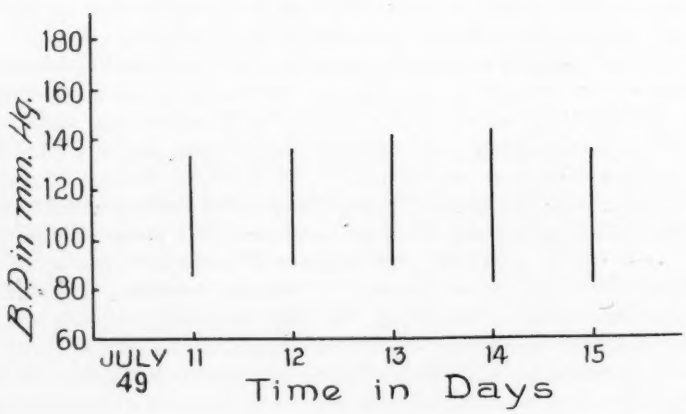

CHART 11

Blood Pressure Effect of Benzodioxane 8 Months Post-Operatively

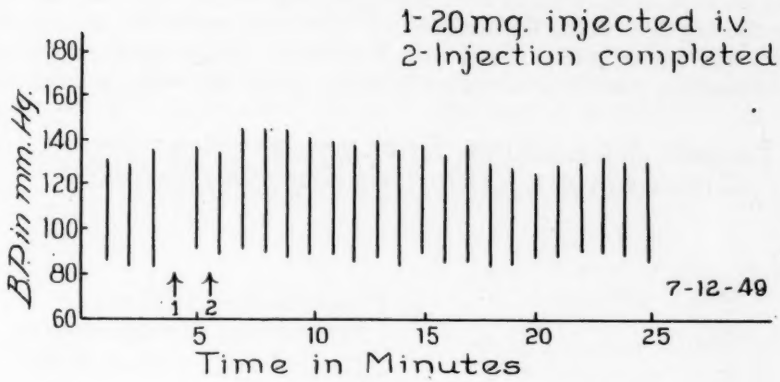

Chart 12

Blood Pressure Effect of Dibenamine ® 8 Months Post-Operatively

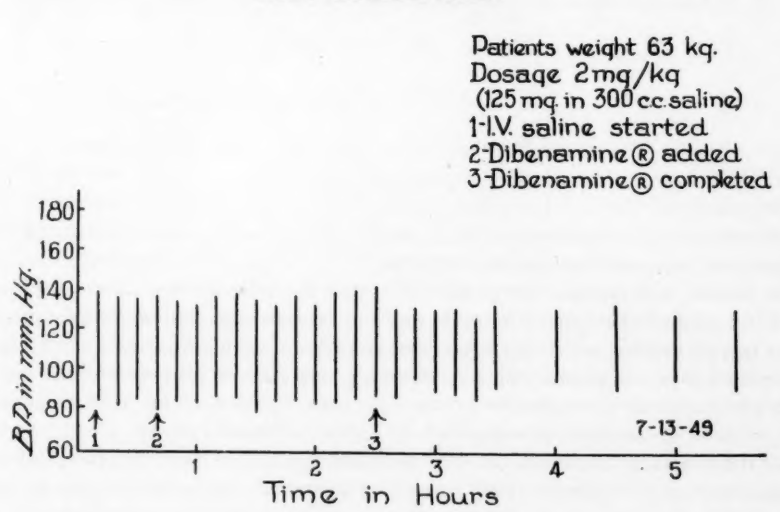

Chart 13

chromocytoma? When dibenamine® is given properly, no great danger is known. Dibenamine® may have some undesirable features when the full blocking dose is employed. The most important are transient psychosis, nausea, vomiting, drowsiness, nasal congestion, convulsions and postural hypotension, as reported in detail by Nickerson and Goodman,[15] and Hecht and Anderson.[16] The recommended dosage in a suspected case of pheochromocytoma should not exceed 2 to 3 mg./kg. body weight. This is half the complete blocking dose. Should the results not be conclusive an additional 2 to 3 mg./kg. body weight may be given in 3 to 4 hours. However, it is usually not necessary to use the full blocking dose. In the case presented, only 2 mg./kg. body weight was used with

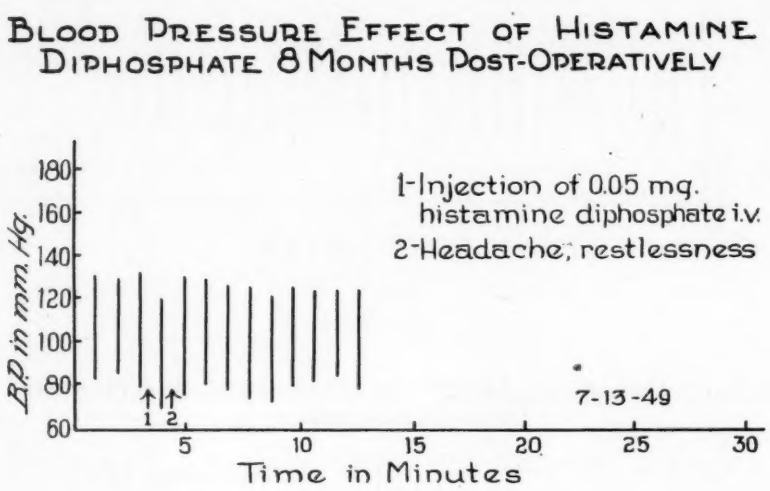

Chart 14

effective results. The effect of the use of this drug lasts from 24 to 36 hours. In considering the use of dibenamine®, one must remember that all patients with or without hypertension will show a fall in blood pressure in the upright position. Therefore, in only those patients who experience a fall in blood pressure in the supine position can the diagnosis of pheochromocytoma be entertained.

In patients with essential hypertension, the use of benzodioxain may cause a slight rise in blood pressure. This pressor response may also be seen when used on normal subjects. This type of response is not seen when dibenamine® is used. Spears and Griswold[13] used dibenamine® in the preoperative care of their patient with satisfactory results. The patients' blood pressure remained normal and the patient gained 4.5 kg. prior to surgery. Hypertensive episodes were also abolished during the preoperative period.

In the past surgery has been the only successful therapy and even then many patients have died during surgery or shortly thereafter, either from a hypertensive crisis or from shock. Many factors are involved, the most common being excessive manipulation of the tumor before the blood supply has been interrupted. Thus a large amount of pressor substance is released with a resultant hypertensive episode which may lead to death. The next most common difficulty is the production of shock after the tumor is removed.

Epinephrine solutions have been given intravenously along with adrenocortical hormones with indifferent results. Dibenamine® has also been used immediately prior to surgery.[13] Probably the patient should be treated much like a hyperthyroid patient—rest, sedation, high caloric diet, not told the exact day of surgery. Then under avertin® with intratracheal ether-oxygen mixture, surgery should be performed. This should prevent excessive stimulation of the tumor and consequently prevent the shock syndrome which may occur when the tumor is removed. Exposure of the tumor and clamping off all arterial and venous channels before the tumor is handled is most important. One should expect an immediate fall in blood pressure which, if the precautions just mentioned are followed, should become stabilized in a few minutes. Epinephrine may be used if deemed necessary.

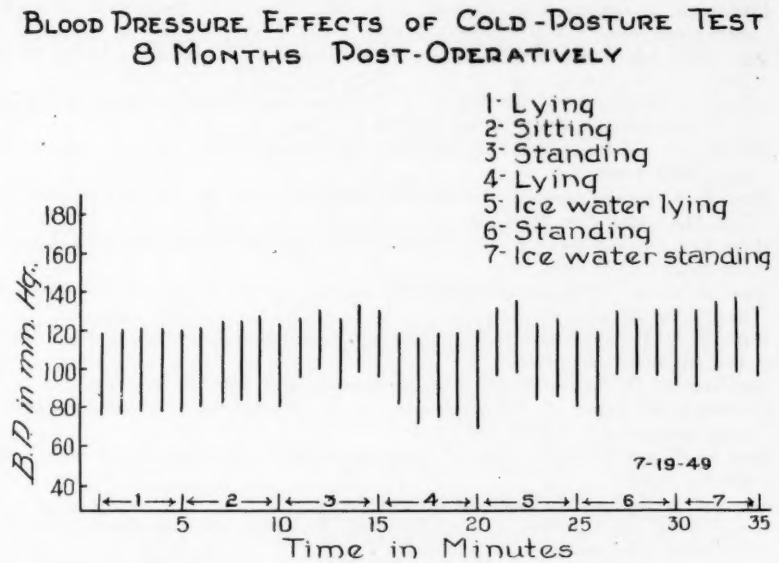

CHART 15

One additional fact, previously pointed out by others,[12] needs re-emphasis; namely, that the hypertension secondary to a solitary pheochromocytoma may persist for many weeks following the removal of this tumor. The hypertension, however, is not high and usually subsides. This is seen in chart 6. This can be readily explained on the basis of secondary but not necessarily permanent changes in the vascular tree. These changes may or may not be reversible, depending on the severity and the duration of the hypertension. This residual hypertension is also correlated with the vascular pattern seen in the eye grounds. These changes were reported by the Ophthalmology Department in this case. The knowledge of this fact is important along with the use of either dibenamine® or benzodioxain in preventing unnecessary surgery on these patients. This is true because the patient might be suspected of having another pheochromocytoma, causing the continued elevation in blood pressure following surgery. The value of the use of these drugs is just as reliable immediately after surgery as it is many months later. This is clearly demonstrated in the case presented.

SUMMARY

A case of a pheochromocytoma in a 13 year old white male is presented. The preoperative and postoperative effects of benzodioxain, dibenamine®, sedation, cold and posture on blood pressure in such a patient are shown. An eight month follow-up study is reported. The fact is re-emphasized that hypertension caused by a solitary pheochromocytoma may persist for many weeks following its removal. It may also return to normal immediately and stay there.

REFERENCES

1. Snyder, C. H. (New York), and Vick, E. H., Hypertension in children caused by pheochromocytoma, Am. J. Dis. Child. **73**:581, 1947.
2. Cahill, G. F., Pheochromocytomas, **138**:180, 1948.
3. Grimson, K. S., Longino, F. H., Kernodle, C. E., and O'Rear, H. B., Treatment of patient with pheochromocytoma, J. A. M. A. **140**:1273, 1949.
4. Roth, G. M., and Kvale, W. F., Tentative test for pheochromocytoma, Am. J. M. Sc. **210**:653, 1945.
5. LaDue, J. S., Murison, P. J., and Pack, G. T., Use of tetraethylammonium bromide as diagnostic test for pheochromocytoma, Ann. Int. Med. **29**:914, 1948.
6. Guarneri, V., and Evans, J. A., Pheochromocytoma: Report of case, with new diagnostic test, Am. J. Med. **4**:806, 1948.
7. Hines, E. A., Jr., and Brown, G. E., Standard stimulus for measuring vasomotor reactions, Proc. Staff. Meet., Mayo Clin. **7**:332, 1932.
8. Hines, E. A., Jr., and Brown, G. E., Cold pressor test for measuring reactibility of blood pressure, Am. Heart J. **11**:1, 1936.
9. Hines, E. A., Jr., Significance of vascular hyperreaction as measured by cold-pressor test, Am. Heart J. **19**:408, 1940.
10. Hines, E. A., Jr., and Brown, G. E., Standard test for measuring variability of blood pressure, Ann. Int. Med. **7**:209, 1933.
11. Smithwick, R. H., Surgical treatment of hypertension, Arch. Surg. **49**:180, 1944.
12. Goldenberg, M., Snyder, C. H., and Aranow, H., Jr., New test for hypertension due to circulating epinephrine, J. A. M. A. **135**:971, 1947.
13. Spear, H. C., and Griswold, D., Use of dibenamine in pheochromocytoma, New England J. Med. **239**:736, 1948.
14. Gould, R. J., Personal communication to the authors.
15. Nickerson, M., and Goodman, L. S., Pharmacology of series of new sympatholytic agents, Proc. Am. Federation Clin. Research **2**:109, 1945.
16. Hecht, H. H., and Anderson, R. B., Influence of dibenamine (N,N-dibenzyl-β-chloroethyl-amine) on certain functions of sympathetic nervous system in man, Am. J. Med. **3**:3, 1947.

SPANISH ABSTRACT

El Uso de Benzodioxaina y Dibenamine en el Diagnostico y Tratamiento de los Pleochromocitomas

Se reporta un caso de un niño de 13 años de edad con hipertension arterial producida por un pleochromocitoma. El diagnostico fué establecido siguiente a la caida de la presion arterial que ocurrió en repuesta a la administracion de benzodioxaina y dibenamine con el paciente en la posicion supina.

Siguiente a la extirpacion de un tumor de 28 gramos localizado en la glandula suprarenal izquierda, le presion arterial bajo a los valores normales, luego comenzó a elevarse gradualmente por un periodo de uno a dos meses, para entonces bajar otra vez a los valores normales. El uso de la benzodioxaina, dibenamine y histamina después de la operacion, a pesar de la existencia de una hipertension moderada no afectó los valores de la presion arterial. Esta ultima prueba siguiente a la operacion es suficiente para demonstrar la ausencia de tumores adicionales y evitar cirujia futura, ya que es sabido que un 10% de estos tumores son multiples.

417 Wysor Building, Muncie, Ind.

Pediatrics

VOLUME 6 AUGUST 1950 NUMBER 2

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

CONGENITAL HEART DISEASE

A Symposium

STANLEY GIBSON, M.D., *Chairman*

CONGENITAL HEART DISEASE FROM THE STANDPOINT OF THE PEDIATRICIAN

STANLEY GIBSON, M.D.
Children's Memorial Hospital, Chicago

DIFFERENTIAL DIAGNOSIS OF MALFORMATIONS WHICH CAUSE PERSISTENT CYANOSIS WITH SPECIAL EMPHASIS ON THOSE AMENABLE TO SURGERY (NOT PUBLISHED)

HELEN B. TAUSSIG, M.D.
Johns Hopkins University, Baltimore

ROLE OF CATHETERIZATION OF THE HEART AND OTHER PHYSIOLOGICAL METHODS IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE (NOT PUBLISHED)

RICHARD J. BING, M.D.
Johns Hopkins University, Baltimore

ANGIOCARDIOGRAPHY IN CONGENITAL HEART DISEASE (MATERIAL PRESENTED AS AN ORIGINAL ARTICLE, PEDIATRICS 6:20, 1950)

JOHN D. KEITH, M.D.
Hospital for Sick Children, Toronto, Ontario, Canada

SURGICAL MANAGEMENT OF CONGENITAL CARDIOVASCULAR ANOMALIES (NOT PUBLISHED)

ALFRED BLALOCK, M.D.
Johns Hopkins University, Baltimore

SURGERY OF CONGENITAL HEART DISEASE

WILLIS J. POTTS, M.D.
Children's Memorial Hospital, Chicago

Presented at the Annual Meeting of the American Academy of Pediatrics, Atlantic City, Nov. 22, 1948.

CONGENITAL HEART DISEASE FROM THE STANDPOINT OF THE PEDIATRICIAN

STANLEY GIBSON, M.D.

A short while ago, I asked a busy pediatrician of long experience how many "blue babies" he had seen in the course of his practice. He thought for a moment, then replied, "Four." Since that time I have made several other inquiries among my pediatric associates and have been surprised to find how small a number of cases of congenital heart disease they have had in their private practice. Yet if some stranger from another planet should visit Dr. Taussig's clinic, he might well conclude that congenital heart disease is as frequent as measles. The concentration of cases in a few medical centers throughout the country has doubtless given a false impression of the frequency and importance of congenital malformations of the heart. If then the problem represents so small a portion of general pediatric practice, one may fairly ask whether the already overworked children's specialist should undertake an additional burden. He is apt, too, to be discouraged when he contemplates some of the special technics and gadgets which have become popular in cardiac diagnosis. Let me hasten to assure him that his feeling of frustration is no more acute than that of many of us of the older generation when some of our chemical pediatricians begin to toss their atomic weights around and overwhelm us with millimols and milliequivalents.

I wish, however, to emphasize the fact that it requires very little time and effort to have a good working knowledge of the diagnosis of most of the congenital cardiovascular anomalies which lend themselves to correction or improvement by surgical means. The field of congenital cardiovascular surgery is in its infancy, and we may confidently expect that the next few years will see many new triumphs in this field. At the present time there are four well recognized conditions in which surgery has proved of undoubted value. These conditions are patent ductus arteriosus, coarctation of the aorta, double aortic arch and congenital pulmonary stenosis.

I wish to say a few words about diagnosis in each of these conditions.

Patency of the ductus arteriosus is diagnosed by the presence of a continuous rumbling or rasping murmur which is usually best heard to the left of the sternum in the second left interspace. Such a murmur is practically pathognomonic of a patent ductus arteriosus. If a murmur heard at the base of the heart is heard only in systole, or if there is only a slight carry-over into diastole, one should be extremely wary in making a positive diagnosis. There are often symptoms and signs which support the diagnosis of patent ductus arteriosus. The majority of these children are somewhat underweight. They are almost always very active, but may tire somewhat more easily than their fellows. The physical examination may reveal, in addition to the characteristic murmur and thrill, a high pulse pressure, a femoral thud and a capillary pulse.

The roentgenogram may reveal cardiac enlargement, a prominent pulmonary cone, and vascular lung fields. A hilar dance is often seen under the fluoroscope. The electrocardiogram seldom shows any marked deviation from the normal.

It is well to remember that in uncomplicated patency of the ductus arteriosus, the shunt is from left to right and that cyanosis is absent. The presence of cyanosis would suggest that there is diminished blood flow to the lungs, and that the open ductus is probably serving a useful purpose in increasing the pulmonary flow. Naturally operation is contraindicated in these circumstances.

There are 2 types of coarctation of the aorta. In the infantile type, the narrowing extends from the origin of the left subclavian artery to that of the ductus arteriosus. The infantile type is usually associated with other serious congenital cardiac anomalies which are incompatible with life for any considerable period. Its recognition is difficult, and surgery has nothing to offer. On the other hand, coarctation of the aorta of the adult type usually exists as a single lesion. It consists of a localized narrowing of the aorta, usually just distal to the origin of the left subclavian artery. In case the constriction of the aorta is marked, the circulation to the lower extremities must be carried chiefly through the collateral circulation. On this account the pulse in the femoral arteries is weak or absent. When this condition is discovered, one should always take the blood pressure in the arms. An elevated blood pressure in the arms practically confirms the diagnosis.

A number of years ago, one of the physicians in the outpatient clinic at our hospital diagnosed coarctation of the aorta in a 2 year old child. He was not a member of the cardiac group, nor was he particularly interested in cardiology. I asked him how he happened to make the diagnosis. He said, "I began about 5 years ago to make palpation of the femoral artery a part of every routine physical examination. This is the first coarctation I have found." If every pediatrician would adopt a similar attitude, few cases of coarctation would be missed. There are some confirmatory symptoms and signs. Headaches are not infrequent. Numbness or heaviness of the feet is an occasional complaint. A murmur is usually heard over the heart but it is not characteristic. Pulsations may be visible or palpable in the intercostal spaces, and a bruit may also be heard. Notching of the ribs seen on the RG is pathognomonic. This sign is rarely seen during childhood.

Another congenital cardiovascular anomaly, which is doubtless more frequent than has been generally recognized, is that of double aortic arch. In this condition the ascending aorta divides into 2 branches, the posterior portion passing behind the trachea and esophagus, and the anterior portion passing in front to unite again to form the descending aorta. Hence the trachea and esophagus are encircled by a vascular ring and may be so compressed as to cause alarming symptoms. The chief symptoms are those of stridor, beginning usually soon after birth, wheezing, metallic cough, difficulty in swallowing and repeated respiratory infections. The diagnosis cannot be made by physical examination. There are no signs referable to the heart. The diagnosis must be made by the roentgenologist and bronchoscopist. In A.P. and lateral films, the barium-filled esophagus shows an indentation at the level of the aortic arch. Likewise the instillation of lipiodol into the trachea or direct observation with the bronchoscope shows narrowing of the trachea at the same level. It is well to remember that symptoms of obstruction to the airway which cannot be satisfactorily explained on some other basis should arouse the suspicion of a double aortic arch. Relief by severing 1 of the limbs of the arch may be a life-saving procedure.

We now wish to say a few words about "blue babies." One of the important factors in the production of cyanosis in congenital heart disease is inadequate supply of blood to the lungs. The most frequent cause of an insufficient flow of blood to the lungs is stenosis of the pulmonary artery. Pulmonary stenosis rarely exists as an isolated lesion. It is found most frequently in conjunction with defect of the ventricular septum, overriding of the aorta, and hypertrophy of the right ventricle. This entity is known as the tetralogy of Fallot. This is the most frequent condition which can be benefited by the Blalock-Taussig operation, which has for its purpose an increase in the blood supply to the lungs.

The typical clinical picture is fairly characteristic. The patient is cyanotic. There is clubbing of the fingers and toes. He is usually underweight, and has been a feeding problem during infancy. He is fretful and unhappy. He walks late. When he has begun to walk, he is able to go only a short distance when he squats on his heels to rest. He may have spells of extreme dyspnea, even unconsciousness or convulsions.

Physical examination of the chest reveals a heart of normal size or only slightly enlarged. A systolic murmur is usually present over the precordium, best heard at about the second or third interspace along the left sternal margin.

RG shows in the A.P. view a heart that is boot-shaped with a concavity in the region of the pulmonary cone. The lung fields show decreased vascularity. The fluoroscopic examination reveals in

the anterior oblique view an unusually clear pulmonary window. Pulmonary pulsations are absent. Right axis deviation is found in the ECG.

Before operation is undertaken, one further bit of information is essential. Experience has shown that in about 20% of cases of the tetralogy of Fallot, the aortic arch descends upon the right. Hence the position of the arch must be determined before the chest is entered. When the arch is on the left, the esophagus is indented upon the left, and vice versa.

Congenital pulmonary stenosis occurs also in another syndrome which, though encountered much less frequently, is sufficiently important to deserve mention. In this condition, tricuspid atresia seems to be the primary lesion. Inasmuch as the tricuspid orifice is completely closed, blood from the right auricle flows through an auricular septal defect or an open foramen ovale into the left auricle, where it meets the blood from the pulmonary veins. This mixture of venous and arterial blood passes into the left ventricle, whence a portion passes through a defect in the ventricular septum into a diminutive right ventricle and on out into a hypoplastic pulmonary artery. There are 2 features which distinguish this malformation from the tetralogy of Fallot. First of all, the left ventricle is hypertrophied, and the right ventricle is small, which produces a characteristic silhouette on the RG. In the second place, the ECG, as would be expected, reveals axis deviation to the left.

We have now touched briefly on the diagnostic features of 4 important congenital cardiovascular anomalies which are amenable to surgery. Diagnosis of uncomplicated patency of the ductus arteriosus is determined by the presence of a continuous machinery murmur, best heard at about the second left interspace near the sternum. Diagnosis of coarctation of the aorta rests upon weak or absent pulsations in the femoral arteries together with elevated blood pressure in the arms. Diagnosis of a double aortic arch depends upon the demonstration of compression of the trachea and esophagus at the level of the aortic arch. This must be done by the roentgenologist, perhaps aided by the bronchoscopist. These diagnoses are easy in the typical case. They can be made by every physician who has an awareness of their possible presence.

Even congenital pulmonary stenosis can be diagnosed with a fair degree of confidence, particularly in older children. Yet it is in the field of cyanotic congenital heart disease that the greatest difficulties in diagnosis arise.

* * *

SURGERY OF CONGENITAL HEART DISEASE

WILLIS J. POTTS, M.D.

The entire subject of surgery of congenital heart disease cannot be covered so I will discuss briefly the 2 most common types—patent ductus arteriosus and pulmonary stenosis.

PATENT DUCTUS ARTERIOSUS

Drs. Taussig and Gibson have outlined the important points necessary for a diagnosis of patent ductus arteriosus. Fortunately the typical case can be diagnosed almost without error. In our series of 52 cases which have been operated upon Dr. Gibson was correct in his diagnosis in every instance.

At present cardiologists generally agree that all typical patent ducti should be treated surgically. The surgeons, however, are not in complete agreement on this question: Should the ductus be ligated or should it be divided and sutured? There are valid arguments on both sides. Presumably, although this has not been proved, the operative mortality is lower following ligation than division. Certainly ligation is a simpler and easier operation than division and suture. However, incomplete closures and later recanalizations follow ligation in a certain percentage of cases. Some surgeons have had none; others report as high as 20% unsatisfactory results following ligation. A ductus completely divided cannot recanalize. Dr. Gross advises division; Dr. Blalock advises proper ligation.

Our experience has been divided between both methods. The first 20 patent ducti, all in children below 14 years of age, were ligated. There was no mortality in this group and to our knowledge there has been no case of reopening of the ductus to date although we anticipate that there will be some recurrences in the future. Nevertheless, the possibility of recanalization and the violation of the sound principles of surgery in burying large amounts of nonabsorbable foreign material in the mediastinum stimulated a search for a safe method of clamping and dividing the ductus.

Well founded fear of uncontrollable hemorrhage due to a slipping clamp has been a great deterrent to the universal acceptance of surgical division of ducti as the operation of choice. Search was made for a clamp which would not slip; which would occlude the ductus but not injure its wall. It is believed that such a clamp is now available. This clamp, described in the *Quarterly Bulletin of Northwestern University,* November 1948, has tiny teeth in the apposing jaws. These teeth, 16 to 1 cm. and each about .5 mm. in diameter, embed themselves in the wall of the ductus when properly placed and will not slip. The hub of the clamp is so constructed that the teeth can be brought just to the point of apposition but not to the point of crushing or cutting the ductus.

With the aid of these clamps 30 consecutive patent ducti have been satisfactorily divided and sutured. There has been no mortality. Although the audience is not interested in the technical details of the operative procedure one point must be emphasized for the sake of the record. No clamp will hold unless the ductus is completely freed from the overlying pericardium and unless loose tissue about the ductus is entirely removed. The most important step in the operation is careful, painstaking and thorough dissection of the ductus. If that is done the clamps will hold and the ductus can be divided with confidence and safety.

Surgical closure of a typical patent ductus is a very satisfactory operation because it restores the heart to normal. The average outside diameter of the patent ducti in this series was 7.4 mm. Children with small ducti usually had minimal cardiac enlargement; those with large ducti, 9 to 12 mm. in diameter, all had rather marked enlargement of the heart and considerable dilatation of the pulmonary artery. Following operative closure of a ductus in a child with cardiac enlargement the heart retains its size until body growth catches up with it. A few children who had very large ducti and huge hearts have a smaller heart now than they had before operation 2 years ago.

The best and safest time for operation is during childhood after 2 years of age.

Pulmonary Stenosis

The desirability of closing a patent ductus arteriosus has just been emphasized and now the formation of an artificial ductus for the relief of pulmonary stenosis will be discussed. A physician after hearing a similar talk on these 2 subjects facetiously commented that half the time I must be crazy. I thanked him for his generosity in allowing any surgeon such a high percentage of sanity. Five or 10 years from now the critic may be absolutely right because by that time we may have an operation which will relieve the cyanosis of pulmonary stenosis by a better method than a shunt between the subclavian or the aorta and a pulmonary artery.

Blalock and Taussig in 1945 roused the admiration of the medical world by their report of an operation by which blood could be shunted to the lungs. They formed a ductus arteriosus by sacrificing the subclavian, innominate or carotid artery and anastomosing its proximal end to a pulmonary artery. All Dr. Smith, Dr. Gibson and I have done is to make a direct anastomosis between the aorta and a pulmonary artery. The object of both operations is exactly the same—the relief of cyanosis due to inadequate blood flow through the lungs.

In order to make an aortic-pulmonary anastomosis a clamp was devised which would fit around the aorta, pinch off a small segment to which the pulmonary artery could be anastomosed and at the same time allow enough blood to flow through the aorta to prevent ischaemia of the spinal cord and possible consequent paralysis.

Selection of patients for operation has been made by Dr. Gibson on the basis of a demonstrated decrease of blood flow to the lungs. No patient has been refused operation even though the outlook for surviving surgery was dim.

The technic of operation is the same as originally described except for one important factor. Whereas originally we made the incisions for the anastomosis in the aorta and pulmonary artery 5/16 of an inch, or 8 mm. long, we now make them 4/16 of an inch, or 6.3 mm. long. These incisions are always carefully measured with a caliper. An incision of 6.3 mm. long in both vessels will form, after the anastomosis is completed, a ductus approximately 4 mm. in diameter. Since it has been found that the smaller opening is adequate for the relief of cyanosis it is routinely used and strongly advised because the smaller the opening the less the cardiac strain.

A question frequently asked is this: Will the anastomotic channel grow as the child grows? We do not know. Will the opening between the subclavian and a pulmonary artery grow? That also is unknown. Experimental studies to date have been inconclusive and sufficient time has not elapsed clinically to answer the question.

The main hazards attendant with this operation are cerebral anoxia and cerebral hemorrhage. About the latter nothing can be done but in the prevention of the former some interesting observations have been made. Dr. William O. McQuiston, the anesthesiologist who has given the anesthetics for all these children, has recently reported hypothermia during operation as a possible aid in lessening hypoxia. The object of this mild refrigeration is based on the accepted theory that a patient with subnormal temperature requires less oxygen than a patient with a fever. Dr. John A. Bigler, with the help of Dr. States of the Central Scientific Laboratory of Chicago, constructed an apparatus for continuous recording of rectal temperatures. Thus far hypothermia, that is, rectal temperatures between 34.2 and 36.7° C. have been maintained during operation in 25 children, seemingly with beneficial results. It seems a bit strange after years of preaching about the importance of keeping patients warm now to advise chilling them during operation. There have been no ill after effects such as pneumonia or upper respiratory infections.

Postoperative complications occur but in general have not been too troublesome. Usually the child goes on to an uneventful recovery or dies during or shortly after operation. We have made it a routine to drain all chests following aortic-pulmonary anastomosis since our early unfortunate experience. Of the first 13 patients 5 required postoperative aspiration of the chest for fluid and/or air. Since routine drainage has been adopted only 4 of 129 patients have required postoperative aspiration of the chest.

Mortality statistics are always of interest because parents are eager to know what chance their child has of surviving surgery. In 142 operations for pulmonary stenosis there have been 19 deaths, an over-all mortality of 13.4%. In 127 patients on whom an anastomosis was completed there were 13 deaths or a mortality of 10.1%. The mortality in 15 operations which were exploratory only—for various reasons no anastomosis could be done—was 40%.

The mortality in relation to age is of statistical interest. In 79 children between the ages of 3 and 16 years there were 4 deaths or a mortality of 5%; whereas, in 48 children between the ages of 3 months and 3 years there were 9 deaths or a mortality of 18.7%. This discrepancy in mortality at different ages is due to the fact that many of these little children were operated upon as an emergency life-saving measure with full knowledge that operation, although offering the only hope, was extremely hazardous.

Results in those 118 patients who survived anastomosis have been extremely gratifying. Cyanosis and dyspnoea have been relieved. Appetite has improved. Dispositions have been truly transformed. Most children have shown some enlargement of the heart following aortic-pulmonary anastomosis. This enlargement manifests itself shortly after operation. Then the heart seems to accommodate itself to the new load and maintains an unchanging cardio-thoracic ratio. A few children have had rather immediate marked enlargement of their hearts following surgery and 2 have gone into heart failure. However, under digitalis both have compensated and are carrying on restricted activity without untoward symptoms.

In conclusion it is well to repeat what we tell each patient. The child has a deformed heart which to date cannot be corrected by surgery. Furthermore, we have added to the heart a new burden of pumping more blood to the lungs. The child will always be somewhat handicapped but should be able to live a fairly normal life if surgery is successful. That the parents are pleased with the results is confirmed by the fact that they are universally deeply grateful.

We have discussed patent ductus arteriosus and advised surgical closure. For the relief of pulmonary stenosis we advocate the formation of a ductus arteriosus by the Blalock or the Potts-Smith procedure. Neither operation is perfect. We aim to make the artificial ductus large enough to relieve the distressing symptoms of cyanosis but not large enough to overburden the heart. We shall not prophesy about the longevity of these children but we do assert that their lives, however long they may be, are transformed from misery to happiness.

Pediatrics

VOLUME 6 AUGUST 1950 NUMBER 2

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATIONS FROM LAWRENCE B. SLOBODY, M.D., FRANCIS F. SCHWENTKER, M.D., AND LULU K. WOLF, R.N., M.P.H.

THE first communication is from Dr. Lawrence B. Slobody, Director of the Department of Pediatrics, New York Medical College, and concerns the recent discussion of pediatric education contained in the May and June issues of this column. His comments on the importance of studying and applying scientific educational principles in the teaching of medicine warrant discussion. An aspect of this problem which has been merely hinted at is the question of recognizing teaching ability and teaching effort as well as research as a basis for academic advancement.

With this issue we present the first two of three invited communications on the Future of Nursing and Nursing Education. The first two are by Dr. Francis F. Schwentker, Professor of Pediatrics at the Johns Hopkins University School of Medicine, Baltimore, and Miss Lulu K. Wolf, Dean of School of Nursing and Professor of Nursing, University of California at Los Angeles.

Next month an article by an administrator of a large public health nursing program will complete the series. These communications have been invited in the hope that they will serve as a stimulant to further comment.

DEAR DR. HARPER:

The discussion on education has been most interesting and helpful. Curriculum, content, research, physical facilities, and other integral parts of the medical schools are all important. However, sufficient attention has not been directed to the teacher and the development of his teaching abilities.

The President's Commission on Higher Education reported, "The most conspicuous weakness of the current graduate program is the failure to provide potential faculty members with the basic skills and the art necessary to impart knowledge to others. Drastic changes of policy may be necessary in many graduate schools if they are to plan teacher preparation studies which will be professionally realistic."

Medical colleges are no better than any of the other graduate schools in their failure to emphasize the development of teaching potential to its fullest extent. For example, a department of a medical school is often judged on its research and publications. This is fine since research should further and stimulate good teaching. In some centers, research has been developed at the expense of teaching. Teaching has become the silent and forgotten partner and has not received proper emphasis.

If we are convinced that teaching is the most important function of the medical school, we must select and train the teacher to develop his maximal teaching abilities. It is interesting to note what has been done in an allied field. Nursing schools are on a lower educational level than medical schools. Yet in all good schools of nursing, it is required that an instructor prepare herself for teaching by taking such courses as the following: Educational Psychology, Principles of Teaching, Physiology of Education, Planning Courses and Units of Instructions, The Modern School of Nursing and its Educational Program, Evaluation and Reconstruction of Nursing Procedures, Student Observation and Teaching in Nursing Subjects, Nursing Supervision in Clinical Subjects, Curriculum Construction in Nursing Education.

I do not know whether we want or need a formalized program such as this in preparing our medical teachers. I do know that study of the principles of education and their application to teaching and learning have the same relationship as our basic sciences have to clinical medicine. If we want to improve our medical teaching, we should not think ourselves above studying and applying scientific educational principles, which have been demonstrated by careful research in that field.

Parenthetically it should be remembered that even a physician, who does not intend to teach in medical school, usually does teach interns, residents, and nurses. Perhaps, even more important, he certainly has to teach and educate patients. For example, parents should be prepared for the care of the child along emotional and physical lines. This is a job that is often neglected or poorly done.

Some time ago, I suggested that consideration be given to integrating the basic principles of education into the medical curriculum, and that graduate seminars in medical education be made available for prospective medical teachers. The time is apparently not ripe for such a far reaching step.

On a more modest scale, it would be an interesting experiment if the pediatric departments would take the lead in the medical school and consider what and how training and supervision might be given to prepare and improve pediatric teachers. Different programs could be set up and tried. This interest and research in medical teaching and education would pay rich dividends.

The American Academy of Pediatrics has done a monumental work in its report on Child Health Services and Pediatric Education. Could not the Academy keep the initiative in planning teacher preparation "To provide potential faculty members with the basic skills and the art necessary to impart knowledge to others"?

LAWRENCE B. SLOBODY M D
New York City

THE FUTURE OF NURSING AND NURSING EDUCATION

THE future of any profession is linked to the potential opportunities in the field. The opportunities are, in turn, influenced by the law of supply and demand. Certainly, at the present time, the demand for nurses exceeds the supply. The increase in demand is the result of: (1) the expansion of fields of public health, industrial hygiene, veterans' hospital facilities, etc.; (2) an increase in the nurse : patient ratio for hospital nursing; (3) a decrease in the hours of work.

The decrease in the supply of nurses is relative since there are more women engaged in nursing today than in the past with the exception of the war years. The relative drop in the number of nursing recruits is due to well recognized economic factors: (1) increased opportunities for young women in commercial fields; (2) low pay for nurses compared with other fields requiring equal or less preparation time; (3) longer hours of work, often on undesirable schedules; (4) lack of benefits such as social security, paid vacations and retirement; (5) a general present-day trend toward selection of "soft jobs" in preference to those offering opportunity for service.

These conditions must be taken into account in any consideration of the future of nursing. Unfortunately, during the postwar period, when these trends were gradually becoming apparent, they were overlooked by the leaders in nursing education who concentrated their attention generally on efforts to elevate the status of nursing to a "professional" level. They contended that the best nursing care could be given only by the nurse who had a broad pre-nursing educational background (as represented by a baccalaureate degree) and whose training included psychological, sociological and other related aspects of patient care. Curricula were set up to include these subjects and the time allotted to bedside nursing experience decreased. There was much talk about the "exploitation" of the student nurse and a demand that nursing education be set up on a university basis. No well informed person would argue against these general principles. There is always a need for persons better qualified in any profession. The best nurse is one who has a broad educational background and who understands the psychological and sociological problems of her patient.

The present problem in nursing supply is, in part at least, caused by the fact that nursing educators hewed too closely to the line of improvement of individual nurses to the professional level and overlooked the economic trends which were making their laudable objective impossible. A sufficient number of college graduates were not willing to enter a profession which held out long hours and low pay as compared to industry, and no social benefits. To rectify these problems would mean an increase in the cost of nursing care which the community could not meet, neither the hospital, nor the patient. The result was an embarrassing void in the area of patient care.

The future course seems clear. Nursing care must be provided and it must be at a cost the community can afford. It must be of the highest quality commensurate with community demand. Since the public cannot afford to employ professional nurses exclusively, nursing activity must be broken down into various areas of responsibility, some of which will require highly trained personnel and others that can be covered by less qualified lower paid workers. Nursing then becomes a group effort.

This premise is now universally accepted by nursing educators. There is still some difference of opinion concerning how it should be accomplished. Without entering into a lengthy discussion of the various possibilities, one plan will be described which seems to

offer opportunity for the best nursing service at a price the community can afford.

Nursing service can be divided into three segments:

1. The professional nurse. She has a broad collegiate education with a university type hospital training. She is the leader in the field and covers the supervisory positions in hospitals, public health and other allied activities. Her salary will be proportionate to her greater ability and qualifications.

2. The registered nurse. The graduates of most nursing schools today fall into this group. They have a high school education supplemented by intensive on-the-job bedside training. The largest share of recruitments needed must be in this group. Therefore, to attract young women into the field, the training period should be lowered to 18 to 24 months, the salary scale remaining the same.

3. Nursing aides. These women will be of the "domestic" type, capable of making beds, feeding average patients, taking temperatures, and attending to many other routine duties not requiring specialized experience.

It will be noted that the "Practical Nurse" has been omitted from this plan. This group, although not new, was developed largely by hospitals faced with acute shortages of registered and student nurses. Women without adequate basic preparation are given a short course in nursing technics and are thereafter free to work independently. The community looks on these women as nurses, which they are not, and fails to understand that they are equipped for little more than maid and companion service. Many states have added to the confusion by licensing practical nurses which gives them a status, the limitations of which are not understood by the public. The wages they receive almost equals the amounts paid registered nurses.

Thus the plan outlined here proposes:

(1) Recognition of a group of highly qualified professional nurses; (2) lowering of the standards of the registered nurse to cover the needs within existing economic limitations; (3) maintenance of all nursing responsibilities under a single system of licensure; and (4) supplementation of nursing care in institutions by employment of nursing aides.

Certain changes in the present structure of nursing education will be needed if this plan should be adopted. The professional and registered nurse groups cannot, in general, be trained in the same area. The former should be the responsibility of the university schools of nursing equipped to offer additional education and training to young women with good educational background. Opportunities for postgraduate work in the various specialties of nursing such as public health, industrial hygiene, pediatrics, surgery, etc. should also be provided since these women will be the leaders and the teachers in the field.

The registered nurse group can be trained in the majority of existing hospital schools of nursing. Most of these are today graduating "trained" nurses rather than "professional" nurses. The only change would be a shortening of the course from three years to 24 or preferably to 18 months.

Nurses aides can be taught in most hospitals by a plan of on-the-job training. No formal courses are necessary. There is no intention of providing aides with a broad experience in nursing to fit them for independent work. Instead they should be employed and instructed for a particular job and, in general, not rotated through various experiences.

It is recognized that the adoption of the plan here outlined would meet certain difficulties: (1) it would be necessary for the various states to change their requirements for nursing registration so as to recognize graduates with 18-24 months' training; (2) the

present body of registered nurses would have to be convinced that such a move would be for the welfare of the community; many believe they would not be recognized as a temporary group between the future registered nurse aand the professional nurse; (3) hospital administrators will protest that by reduction in the training time they would lose the free services of student nurses during the period they are most valuable.

It may be that some of the difficulties cannot be entirely overcome. Nevertheless any plan for the future of nursing service and education should be aimed at the optimal situation.

What has been written here may sound like a physician's criticism of the foresight of nursing educators. It is meant to be a constructive analysis of the present situation. At the same time, it should be pointed out that the foresight of the medical profession is not without reproach in problems of its own.

FRANCIS F. SCHWENTKER, M.D.
Baltimore

THE FUTURE OF NURSING EDUCATION

THE current demand for community nursing service has focussed attention upon the profession of nursing—its fields of activity, its educational aims and its plans for the future. Those who have studied the problem believe that a shortage of personnel exists and they agree that something must be done about the structure of nursing and particularly its educational base if the profession is to produce the quantity and quality of nursing personnel needed.

Nursing education, from the very beginning, has been outside the domain of institutions of higher learning. Since 1873, when the first schools of nursing were established in this country, nurses have received their education in hospitals through an apprentice-like plan of training-on-the-job. Unlike the endowed educational institution, established by Florence Nightingale at St. Thomas's Hospital in London, the American adaptations of the Nightingale School were set up to provide nursing service to patients in hospitals rather than to educate students for the profession of nursing.

For the past 50 years, leaders of nursing education have struggled to modify this plan and create an economically sound system of nursing education. Numerous surveys and studies have been made to determine the weaknesses of the apprenticeship system and suggestions have been offered regarding the nature of the educational program needed to prepare the nurse for community nursing service.

Three decades ago, when the subject of public health nursing was attracting attention in the United States, the Committee for the Study of Nursing Education recommended a reorientation of nursing education to meet new health and social goals. In the Report[1] of this Committee, published in 1923, the remedies suggested were to enrich the curriculum to provide for the inclusion of the social and health aspects of nursing, and to place the nursing school under the aegis of the university. The collegiate nursing school, as described in the Report, was to be an integral part of the university and its program and administration were to conform to university standards.

Publication of this report led to the establishment of a few university schools but it failed to bring about any widespread change in the system of nursing education.

Ten years later, the Committee on the Grading of Nursing Schools again emphasized

the need for placing the education of nurses on a collegiate level. The final report[2] of this Committee urged that nursing curricula be strengthened and expanded to include theory and practice in all clinical areas and advocated the development of university nursing programs to safeguard the professional status and freedom of the school.

During this same period the Committee on the Costs of Medical Care struck at the nurse's preparation and pointed up the fact that the traditional hospital training course would no longer suffice for the education of the nurse. In the majority report[3] of this committee it was urged that nursing education be thoroughly remoulded so that nursing schools would produce well qualified, socially-minded nurses with a preparation basic to all types of nursing service. "The care of hospital patients," said the Committee, "is not, in and of itself, sufficient preparation for professional nursing."

The Survey of Public Health Nursing,[4] conducted by the National Organization for Public Health Nursing, furnished additional evidence of the fact that nursing schools were failing to provide an adequate basic preparation for all fields of nursing.

The data collected in this survey gave substantial support to the statements of previous study groups and highlighted the fact that nursing schools put too little emphasis on the preventive and teaching aspects of nursing.

Reports and deliberations of later, more specialized groups showed similar findings and recommendations. All pointed to the need for better preparation of nurses in the basic program and all urged the development of university schools.

These committee findings, with their revelations of failures and shortages and their recommendations for improvements, were responsible for a few advances in nursing education and nursing service but they were not sufficient to place nursing on a sound educational basis. The majority of nursing schools continued to function under the apprenticeship plan and failed to supply nurses qualified for community health service.

Concerned that this system of nursing education could not meet the demand for the quality or quantity of nursing personnel needed and hopeful of a critical assessment of nursing education similar to Dr. Abraham Flexner's assessment of medical education, the nursing profession commissioned a study of nursing education early in 1946 and appointed Dr. Esther Lucile Brown to conduct it.

The purpose of the study was to determine, if possible, who should organize, administer and finance professional schools of nursing. Early in the stages of planning, it was agreed that nursing service and nursing education should be viewed in terms of what was best for society at large—not what was best for the profession of nursing as a possibly "vested interest." The director was given full control of the project with freedom to travel where she would; consult with physicians, hospital administrators and others as she pleased; investigate schools as she saw fit and prepare a report that revealed the facts of the situation.

During the course of the study, lay and professional committee groups were created for advisory purposes; administrators of schools and hospitals were called into conference as needed; physicians, nurses, citizens and educators were queried; previous nursing reports were reviewed; health legislation was studied and some 50 schools were visited. When the study was completed in 1948, two thousand persons had had a part in it, and the conclusions and recommendations had a familiar ring. This time the ring was loud enough to be heard and there was no mistaking its tune. The apprenticeship system of nursing education had not and could not produce nurses qualified for community nursing service.

In the published report[5] of this study, it was made clear that the shortages in nursing personnel and the gaps in nursing service were due primarily to an outmoded system of nursing education. The use of students to provide hospital labor, on the one hand, and the lack of enriched university programs of nursing education on the other, were the two factors believed to be responsible for the qualitative and quantitative shortages in nursing personnel.

With the maintenance of health rather than the cure of disease as the future goal of medicine, and with great expansion in the nation's health programs and hospital services, it is obvious, said the author of the report, that a greatly increased nursing competence will be demanded in the future and an enormous supply of nursing care will be needed. To solve this problem of supply and demand, it was recommended that the nursing power of the country be supplemented at the bottom and the top and that measures to do this be instituted immediately.

The task of the future, according to Dr. Brown, was to emphasize nursing and nursing functions rather than nurses. Once this was done, she pointed out, a functional system of nursing could be fashioned and persons of many different skills could be trained to render efficient service in the area of health services.

If it is agreed that this is a sound plan of action for the future, nonprofessional nursing personnel—practical nurses—must be prepared now to care for the subacute, convalescent, and chronically ill patients. And, if practical nurses are to assist professional nurses with the care of acutely ill patients, large numbers should be recruited for these practical nurse programs. The first line of attack on the nursing problems of today is probably in this area. These training programs can be introduced rather readily into adult and high school systems of the country. It only remains for nursing and allied professions to introduce them. Funds are available from the United States Office of Vocational Education to finance such programs now, but the funds are earmarked for home economics and agriculture. When community groups and the professions are successful in having the funds for these programs made directly available without having to clear through home economics or agriculture, the programs will naturally get under way faster.

Hand-in-hand with the initiation of these practical nurse training programs, must go licensure for regularizing and legalizing their status and for protecting the standards of the nursing profession. Any legislation that is passed must provide for the registration of practical nurses who are functioning successfully now under supervision but who have had no formal training.

Simultaneously with the development of these programs for the nonprofessional nurse must go enriched training programs for the professional nurse. These programs, according to the Brown Report and others, should be placed squarely in institutions of higher learning. This would result in the upgrading of the professional nurse's preparation and should lead to the development of large and genuine schools of nursing. Expansion of facilities for collegiate nursing education may be difficult and will, of necessity, be slow but as nursing leaders give to them their concentrated attention and as parent universities provide them with the resources they require, top ranking schools will be developed. Public as well as private support for professional nursing education is needed and it behooves the citizens of this country as well as the nursing profession and the universities to see to it that funds are forthcoming. In the future, it is probable that official bodies—local, state and federal—will concern themselves with supplying the additional resources needed for the support of nursing education on the professional as well as on the nonprofessional

level. When support of this type is available, it will be possible to build nursing schools in universities and colleges comparable in number to existing medical schools. And like medical schools, these nursing schools will be sound in financial structure and organization, adequate in faculty and facilities, and distributed to serve the needs of the entire country.

During the period of transition, it will be necessary to continue to train the group of workers now known as registered nurses.[6] In light of the overlapping and wastefulness of the present curriculum offered these nurses, it is essential that these programs be cut from a three year to a two year period. Experimentation with shortened hospital nursing programs is going forward at present and the results of these studies will soon be at hand.

Assuming it is agreed that the educational program for the professional nurse should be moved to the university and should undergo revision and reorientation to include the social, emotional, and health aspects of nursing, how is this content to be incorporated? How can it be arranged? What revision is believed to be necessary?

The curriculum revision needed to prepare the professional nurse for community service adds up to something just short of a revolution. It involves rethinking and reorientation of every course; expansion and strengthening of the health and social sciences; provision for planned field trips to community health and welfare agencies; visits to patients' homes in the urban and rural areas; guided practice in the care of patients and their families in the hospital, outpatient department and home; and guided practice in analyzing and meeting the patient's mental, physical, social and emotional needs.

Such expansion and reorganization of the nursing curriculum cannot come about overnight, nor can it be the work of any one person or group of persons. The entire faculty of each school must assume this responsibility and, when necessary, seek the advice and consultation of public health specialists, medical and nurse educators, sociologists, psychologists and curriculum experts.

The specific lines along which this revision and reorientation will take place in any one school cannot be predicted. Each institution is influenced and limited by its past history, its geographic location, its resources and its present leadership. Each must capitalize on its own experience and its own unique opportunities. Planning and group thinking are needed in every case and nursing leaders with vision must initiate the action.

What does it mean to revise a curriculum, justify its content and decide whether or not it is of value to the student? It means relentless scrutiny of each course offered to see if the subject matter is pertinent and is serving the individual student by helping her gain ability to solve the day-to-day problems she encounters.

The course in psychology for instance, what is its function? Does the student learn the facts underlying human behavior, see how behavior can be explained and to what extent it can be controlled, and predicted? Does she really understand that behavior is learned and that some individuals are "quicker" to learn than others? Does she give evidence of that understanding by an increasing efficiency in making her own adjustments and in modifying her established patterns of reaction? This knowledge put into practice for herself will help her in understanding the meaning of her patient's behavior and thus she will have clues as to how to approach him, how to establish rapport and how to initiate appropriate measures to help him make a satisfactory adjustment to his illness. Tolerance comes with understanding. The nurse student will be more tolerant of difficult patients or patients with personality disorders if she understands motivation and the process by which biological drives condition human behavior and adjustment.

The study of sociology and the field of social work with the related observations and field trips in the community, what do these courses contribute to the preparation of the nurse? Does the nurse student need to learn about man's social life or be concerned with the life of man in groups?

In her study of sociology and social work the student becomes accustomed to viewing the community as a system of interrelated and interfunctioning institutions, which create a web of human relationships and which help to condition or pattern human behavior. Through her contacts in and about the community and her observations or field trips, she should become aware of the formal and informal methods of social control and the distributive character of the community's population. When she sees the way in which a community acts upon individuals and families, locating them in different divisions of the community and creating barriers, each of which conditions the way people live, she should have a better understanding of class and caste and their relation to social problems. If she can get the feel of what the anthropologist or sociologist calls culture and if she can see a given culture as a system of related traits, she will be able to recognize culture traits in her patients and their families and relate them to their specific patterns of behavior. Because she deals with all races, classes, and creeds, she must learn to relate culture traits to social status, behavior patterns, and physical and mental health. If she doesn't learn this, her health guidance and nursing care will be irrelevant, perhaps worthless, certainly wasteful of her time and others.

Preventive medicine and public health—do these courses belong in the basic nursing curriculum? Are they essential to the student's preparation for nursing? These studies deal with the causes and treatment of disease and the ways in which disease may be reduced, alleviated, or completely eradicated. Study of this content along with observations of the different community health agencies helps the student to see the relation of her work to the welfare of society. She sees illness as the result of overcrowding, poverty, ignorance, and malnutrition and she also sees it as the cause of social problems and family maladjustment. If the nurse student is taught the facts regarding the health and sickness data of the community in which she is to function as a student she can direct her efforts toward reducing that sickness and improving that health. If she doesn't know the health statistics of the community, her work of prevention and cure will have little relation to the over-all health and welfare needs of the community and can at best be only fragmentary.

If the student is to gain this philosophy of nursing for health, many learning experiences related to her own health and the health of others must be placed early in the curriculum. Before the student attempts to enter the hospital situation to learn how to analyze and meet the health needs of others, she must know how to analyze and meet her own health needs. Health knowledge put into practice for herself will serve as a base in understanding the health needs of others and in guiding them to better health practices.

In addition to acquiring this knowledge of health and healthful living, the student should understand how social and economic factors promote or retard health and how they influence disease. Thus, she should be given an "opportunity to have guided visits to patients in their homes, and be helped to see the interrelationship between illness, housing, leisure time activities, working conditions, nutrition, economic status, education, mores and customs, cultural traits, and community health practices."[7] To give her this concept takes time and it also requires enrichment of the social sciences with related com-

munity observations and guided visits to the patient in his home. Not until the student learns that nursing is health conservation as well as service to the sick is she ready to enter the hospital to learn how to give comprehensive nursing service to the sick.

During the clinical period of the student's experience she learns the care of patients in the wards of the hospital, the clinics of the outpatient department, the health centers, and the homes of the community. These experiences should include the care of patients with mental illness, with medical and surgical conditions, and with conditions that are communicable. They should also include the care of the obstetric patient and the care of the child. To provide a truly educational experience for the student and to safeguard the patient and his family, these learning experiences must be under the guidance of qualified nurse faculty members who are free to teach. With the help of these graduate nurse experts the student should learn how to analyze the patient's needs and how to plan and execute a program of care designed to meet those needs. This experience in the care of the sick would include learning how to modify the patient's diet; to safeguard his expenditure of energy; to provide for his personal cleanliness and his needed rest and recreation; to encourage his return to health and activity; and to guide him in planning for and carrying out a program of activities designed to facilitate his recovery and rehabilitation.

During the course in obstetric nursing, the student should learn how to care for the mother and baby during pregnancy, labor, delivery, and the puerperium. Since maternity is a natural physiologic process, the emphasis of the teaching in this nursing area should center upon the promotion of health and comfort for the mother and baby and the prevention of illness or injury. While learning how to give meaningful, safe maternity care, the student should also learn how to help the obstetric patient meet her day-to-day problems and adjust her life to meet the needs of her mind and body, her baby's needs and the needs of her family. This help should be provided to the mother in individual conferences at the bedside and in the clinic and in a series of planned and guided group teaching activities.

In like manner, the study of pediatric nursing should give the student an understanding of the child, his physical, mental, emotional and social growth and development. With the help of qualified pediatric teaching personnel, the student should learn how to provide comprehensive nursing care and supervision to prematurely born infants, full term infants, children of the preschool age and those in the school age groups. These learning activities would take place in the hospital's pediatric service, the well baby clinic, sick baby clinic, child guidance clinic, convalescent home, and the homes of children in the community. Opportunity to work with children in normal life situations should be provided through directed observation and planned participation periods in schools, nursery schools, homes and health centers. Since the welfare of the child is dependent upon the care he receives from his parents, the student should also have guided experience in interpreting to parents and to other responsible persons the needs of children and the measures essential to provide for them.

Finally, to round out these learning experiences and to help her learn how to apply all of her knowledges and skills, the student should be given a concentrated period of guided nursing practice in a community health program. During this experience she would learn how to adjust her nursing technics to the home situation and how to guide the family in its efforts to secure and maintain health. She would also secure needed

practice in cooperating with other members of the health team in utilizing community resources to help families meet their needs.

The optimum time required for this enriched program of nursing education is not now known. The university curricula being offered to nurse students today vary from less than four calendar years beyond high school graduation to 2½ calendar years beyond college graduation. Experimentation with time plans is needed and some is going forward. More is needed and more will be started as schools established within universities embark upon these enriched programs. The best answer to the curricular pattern and the time plan can only be found through research and in terms of how long it takes to prepare the professional nurse to give quality nursing for community service.

Programs of nursing education such as have been described here can be organized and administered in several different ways. All of these ways must provide for a clarification of the costs and a division of the activities concerned with nursing education and hospital nursing service. The care of patients will continue to be learned in the hospital but students will learn that care under different circumstances. Qualified nursing instructors who are free to teach, will guide the students and the students will be freed from nursing service responsibilities so that they have time to learn. Like the medical student, the nurse student will pay for her education in tuition fees and will carry no hospital nursing service load. If the student should work in the hospital during one of her free evenings or over a weekend she will be paid for her nursing services.

Arranging the clinical period of the student's educational program in this way separates nursing education from hospital nursing service and makes it possible to clarify the costs of each. Once this step is taken, it is comparatively simple to determine what will be needed in the way of tuition, endowment, and tax funds to finance nursing education. Through scholarships and payment for student service, the cost to the student can be held to a reasonable figure. Through endowment, private gifts, and tax funds the cost to the school can be greatly reduced.

Nursing for the future will be performed by two legally distinct groups of workers within the profession—the professional nurse with collegiate training and the licensed practical nurse with approximately one year of vocational training. The division of the nursing function and the preparation of two groups of nursing personnel is far from an easy task. Tradition is strong and emotions run high as medical, hospital, and nursing groups gather to talk, to plan and to initiate action. This is the only way, however, that concerted action can come about. The road ahead is narrow and rough. If all groups concerned can view these problems objectively, that same road may become wider and smooth. As relations are clarified and improved between the nurse, the doctor, and the other members of the health team, blueprints for action will be drawn and the nursing profession can set about to put its house in order.

The improvement of nursing education is imperative if nursing service is to be improved. It is imperative for the welfare of the people of the nation and the security of hospitals and health centers. The sooner this fact is faced, the better it will be for all concerned—those concerned with health and medical care programs and those concerned with nursing.

LULU K. WOLF, R.N., M.P.H.
Los Angeles

References

1. Goldmark, Josephine, Nursing and Nursing Education in United States, New York, The Macmillan Company, 1923, p. 11.
2. Nursing Schools Today and Tomorrow, Final Report of the Committee on Grading of Nursing Schools, New York, 1934.
3. Medical Care for American People, Final Report of the Committee on the Costs of Medical Care, Chicago, University of Chicago Press, 1932, p. 142.
4. Survey of Public Health Nursing, New York, Commonwealth Fund, 1934.
5. Brown, Esther Lucile, Nursing for Future, New York, Russell Sage Foundation, 1948.
6. Program for Nursing Profession, Report of the Committee on the Function of Nursing, New York, The Macmillan Company, 1948, p. 62.
7. Wolf, Lulu K., Nursing, New York, D. Appleton-Century Company, 1947, p. VI.

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

THE UNITED NATIONS INTERNATIONAL CHILDREN'S EMERGENCY FUND

IN THE "Economic Cooperation Act of 1950," Congress has included an authorization of $15,000,000 with broad authority to the President to make contributions to the United Nations for international children's needs in the fields of health and welfare. Congress indicated that it expects the President "to use his authority prudently with a view to actual needs and to the desirability of the earliest practicable transfer of the international children's welfare programs concerned from the present temporary agency to a permanent arrangement within the United Nations framework." Thus Congress has taken an important step to assure continuation of the work of the United Nations International Children's Emergency Fund (UNICEF) which is so essential to millions of the world's children.

This Fund, cooperating with foreign countries, has been most effective in helping to supply milk or a daily supplementary meal to many millions of children and pregnant mothers. In cooperation with the U. N. World Health Organization, the Fund has undertaken with the Danish Red Cross and its Scandinavian associates a mass antituberculosis BCG vaccination program for European children. This campaign is unprecedented in the international public health field and should eventually yield results not only in the reduction of tuberculosis on a vast scale, but also in adding greatly to our knowledge of BCG vaccination.

The U. S. Committee for UNICEF held a special meeting in New York on June 8, 1950. In this meeting, members of the U. S. Committee were joined by liaison representatives of governmental and nongovernmental organizations to discuss the present status of the Fund and the long-range activities for children. From the mimeographed minutes of this meeting, the following excerpts are taken.

Miss Katharine F. Lenroot, U. S. representative to UNICEF, was unable to be present. Mrs. Oswald B. Lord, Chairman of the U. S. Committee, read the following letter from Miss Lenroot, which summarized the current status of the U. S. position in regard to UNICEF:

"I am very sorry indeed that unexpected developments requiring my presence in Washington make it impossible for me to attend your meeting tomorrow. Will you please express my regret to the group.

"I am very happy about the provisions in the U. S. Foreign Economic Assistance Act of 1950 relating to International children's welfare work. I am delighted that President Truman in his statement on the signing of the Foreign Aid Bill gave recognition to

the magnificent work of the United Nations on behalf of children. I am sure your Committee will be glad to note this paragraph in his statement, which refers to the fact that the Act will enable us to support new and permanent arrangements under which the United Nations can deal with the continuing needs of children, and in the meantime can give such support to the present Emergency Fund as may be needed to prevent a lapse in this essential work.

"At a conference held in the Department of State today, participated in by Mr. Hickerson, Assistant Secretary of State, and other members of the staff of the State Department, and by Mr. Pate and members of his staff, it was unanimously agreed that the work inaugurated by the Children's Fund should go on without interruption through an orderly transition period, and that such amounts should be released by the President from the $15,000,000 which, it is hoped, will be appropriated by the Congress for children's work, as will insure that there is no hiatus in contributions from other countries or in allocations needed to carry on going programs. A target of January 1, 1951 as the time when it is hoped the permanent arrangements can be perfected seemed reasonable to all, as this will give time for action by the Economic and Social Council and the General Assembly.

"The matter of immediate and pressing consideration is the inclusion of the full amount of the $15,000,000 authorized in the Appropriation Act.

"I believe that the United States Government has given full assurance of its desire to support continuing coordinated programs for children by the United Nations with the cooperation and technical help of the specialized agencies. The program of the United Nations Children's Emergency Fund has already shifted its emphasis in a major way from emergency feeding to technical aid and supply programs, carried out in cooperation with the specialized agencies. The United States is fully aware of the importance of provisions by which the highest caliber of leadership for the program for children and necessary staff arrangements can be assured."

Mrs. Lord introduced Mr. Walter Kotschnig, Director, Office of the United Nations Economic and Social Affairs of the Department of State. In opening the discussion on United States recommendations with regard to child welfare activities within the United Nations, Mr. Kotschnig stated that the United States is deeply concerned with putting the work for children, so excellently begun by the Children's Fund, on a permanent basis. The Executive Branch believes that the present long-range programs now being undertaken by UNICEF constitute a contradiction in terms within an "Emergency Program" and that now is the time to create an organization that will meet the continuing needs of children. To this end, this government has made the following proposals in order to integrate activities on behalf of children more closely into the United Nations:

a. That the U. N. Social Commission, with the addition of up to four other representatives from nations belonging to the United Nations, compose a Children's Board to deal with policy matters. The Social Commission was recommended because under its original terms of reference this body regularly deals with questions of child welfare and family problems.

b. That a Committee at the Secretariat level, composed of representatives of specialized agencies (such as WHO, FAO, UNESCO, and to some extent ILO) and of the Secretary General plan the program in detail. This would be an extension of UNICEF's present policy of coordinating its work with that of WHO and other agencies.

c. That there should be an organizational set-up within the U. N. Secretariat to serve the Board and the Committee.

d. That the financing be under the U. N. budget through a special account, consisting in part of an allocation from the regular U. N. budget and in part of voluntary contributions from governments and peoples. All countries should be interested in the welfare of children, and each country should contribute according to its means. By making the budget for child welfare activities part of the U. N. budget, there would be an assured minimum income to guarantee the permanency of the program.

Mr. Kotschnig stressed that there must be no hiatus between the magnificent work which UNICEF has done and is doing, and the creation of a permanent agency. He went on to say that the Congress of the United States has authorized an additional $15 million to be used for international child welfare and that the Department of State is requesting that the full amount be appropriated. How much of the total should go to UNICEF depends on how much money the Fund receives during the next six months from other sources and upon the maturing of certain of its programs now in process. It is expected that a fair amount of the $15 million will be unspent at the end of the year and available for allocation to the permanent organization.

Mr. Kotschnig pointed out that there are, and will for many years be, tens of millions of children who are undernourished and that their problem is not an "emergency" but a sad and permanent problem. To secure the billions of dollars required to carry on world-wide mass feeding programs is beyond the realm of possibility. For that reason, this government recommends large-scale demonstration projects, backed by adequate supplies, and preventive medical and training programs which will have a curative and lasting effect. It is understood that such programs would be undertaken only when the recipient government has given assurance that it will carry on the programs once their effectiveness is shown. The United States plans to resubmit its proposals at the Economic and Social Council meetings in July because it feels that voluntary contributions to UNICEF are apt to diminish in the next few years and that it will be much more difficult at that time to shift successfully from a temporary to a permanent program. Later in the discussions it was made clear that the United States plan includes provision of funds for outright relief in catastrophic situations, such as the Ecuador earthquake, the Palestine refugee tragedy, etc. The question was raised as to whether it was realistic to expect other countries to increase their contributions to the U. N. budget at a time when many of them are reducing their international expenditures. Mr. Kotschnig conceded that it may not be possible to get all that is desirable, but contended that it is important that a fixed amount be available annually as a minimum on which programs could be planned. It was suggested that setting up a new board to replace UNICEF would not answer the criticism that U. N. is "over-organized," but Mr. Kotschnig replied that the new plan would provide closer coordination, less duplication, and greater administrative efficiency than is possible under the present machinery. Both Miss Frances Kernohan, Department of State, and Mr. Kotschnig emphasized that it is the intention of this government to continue supporting UNICEF until the new organization is able to undertake its work following a period of gradual and orderly transfer of functions. It is expected that the staff of the new organization will to a large extent be comprised of the present UNICEF staff, including the supply staff.

At the invitation of the Chairman, Major General Lowell Rooks, UNICEF, stated that

he was in general agreement with the United States position, provided that the experienced staff of UNICEF be retained for the new organization and that the transition be smooth. He is of the opinion that there is a distinct advantage to "UNICEF" as a name because of the enviable reputation it has earned in other countries. General Rooks reported that 42 countries are presently contributing to the Children's Fund; that approximately $28 million has been received by the Fund during the last 12 months of which $19 million came from the U. S. Treasury under the matching formula, and $3 million came from voluntary campaigns around the world. He said that this compared favorably with amounts which the Fund has received in other years.

Miss Kernohan, Department of State, in reply to a question about the possibility of agreement being reached at the Economic and Social Council meetings in July between the United States position and the proposal adopted by the Social Commission, stated that the two positions are not irreconcilable. In order to facilitate discussion of the question, the Department of State has circulated a rationale of its position to U. N. delegations of interested countries, U. S. missions abroad in interested countries, and to U. S. representatives participating in conferences of the specialized agencies concerned. It is believed that a workable compromise can be achieved which will safeguard the welfare of children in the future.

The Chairman, having noted that her annual report had been circulated to the representatives of organizations as well as to the members of the Committee, added the following subsequent developments:

a. Contributions received from within the United States since January 1, 1949 have now exceeded $200,000.

b. The National Motion Picture Association's report shows 4,141 bookings for the one-reel version of "For All the World's Children." This is an unusually high figure for a noncommercial film.

c. Additional magazine publicity includes an editorial in the May issue of the *Ladies Home Journal,* a box by Irene Dunne in the May issue of the *Woman's Home Companion,* copy and photographs in five trade magazines and one school administrator's publication, and material prepared for fall issues for approximately 15 other publications. The editorial in the *Ladies Home Journal* has brought in 132 contributions totaling $1,466.50.

The Chairman requested all representatives of organizations to enlist the help of their memberships in writing or telegraphing to the members of the Senate Appropriations Committee, urging that the full $15 million authorized by the Congress in S3420 Foreign Economic Assistance Act, 1950, Title V, International Welfare Activities for Children, be appropriated.

Following an expression of appreciation by the Chairman for the splendid support which the organizations have given to the program of the U. S. Committee, the meeting was adjourned.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

CONGENITAL SYPHILIS

The problem of syphilis in the adult population showns signs of yielding to the vigorous attacks aimed at it from many directions during the past decade. The increasing use of penicillin as a therapeutic agent, the intensified case-finding activities and widespread educational programs directed by the Public Health Service and State health departments, have been accompanied by a gratifying decrease in reported cases of primary and secondary syphilis. There has been a smaller but definite decrease in the incidence of early latent syphilis. Infant deaths resulting from syphilis show steadily declining rates, as does syphilis mortality among the general population. Admissions to mental institutions show a smaller proportion of cases with psychoses growing out of syphilis.[1,2]

With this favorable picture of syphilis in the general population, it would be reasonable to expect a decline in number of cases reported as congenital syphilis. Such is not the case. The number of reported cases of congenital syphilis has remained constant for the past 5½ years. Approximately 14,000 cases have been reported each year. About half the congenital syphilis reported is found in children 10 years of age or under, about 37% in children age 4 or under, about 20% in babies under 1 year of age.

In addition to the reported cases, the Public Health Service estimates that some 100,000 children in this country, 10 years of age or under, have undiscovered congenital syphilis.

Armed as we are today with satisfactory serologic tests for the detection of syphilis and with penicillin widely available as an effective therapeutic agent, congenital syphilis should not occur at all. A concerted effort of general practitioners, obstetricians, pediatricians, hospitals and health departments through their programs for maternal and child-health services and for venereal disease control, could result in eradication of the disease. Certain procedures,[3] we believe, would help to reach this goal:

1. At least two blood tests for syphilis should be made as a routine part of every woman's prenatal care—one early in pregnancy, the other late in the third trimester or at time of delivery.

One blood test during pregnancy has long been an accepted procedure and has even been made compulsory by law in a number of States. However, a woman's serologic test may be negative early in pregnancy and later become positive, either because she was in the incubative phase of the disease at the time of the first tests or because she acquired an initial or recurrent syphilitic infection later in pregnancy. Heyman and McCain[4] recently reported that about a fourth of the 77 women who delivered syphilitic infants in their series had positive serologic tests by the time of delivery or one or two weeks post partum, although the tests had been negative earlier.

2. A pregnant woman with untreated syphilis is a medical emergency and should receive treatment at once.

Adequate treatment of the infected mother is nearly 100% effective in preventing con-

From the Children's Bureau, FSA, Social Security Administration, Washington, D.C.

genital syphilis in her baby. There are, in the literature reviewed before January 1, 1950,[5] reports of more than 850 pregnant syphilitic women treated with various types of penicillin and several different dosage schedules. These pregnancies resulted in 14 living syphilitic infants, a failure rate of 1.5% which compares very favorably with the expected rate of cure of syphilitic men or nonpregnant women. The failure rate with penicillin can be still further reduced, perhaps to zero, by adequate prenatal care of the mother so that (1) her infection may be recognized and treatment given before the fetus is infected, or so that (2) re-treatment may be given to patients who have failed to respond satisfactorily to the initial course of treatment or to those who develop an infectious relapse or a re-infection late in pregnancy.

3. For those mothers who receive no prenatal care prior to delivery in hospitals, a blood test should be done at time of admission. If the test is positive, the mother should be treated. Treatment of the mother, even immediately before delivery, offers some protection to the baby.

4. For all babies born of untreated or inadequately treated syphilitic mothers, a blood test for syphilis should be made as soon as possible. (The new filter paper microscopic test[6] promises to be satisfactory and to eliminate the difficulty of obtaining venous blood from a baby.) A positive test of the infant's blood may not indicate the presence of syphilis; similarly, a negative test may not indicate the absence of syphilis. If the chances are not good that the physician will be able to observe the infant over a minimum period of four months, he may wish to give protective penicillin therapy.

Protective therapy requires a dosage adequate to cure syphilis, if the baby should be infected. When aqueous penicillin is used, the present recommended schedule[5] is 100,000 units/kg. body weight given in divided doses of 120 injections at three hour intervals. Delayed absorption preparations have not been sufficiently used in children to determine the optimum schedule of treatment. However, clinical trial of these drugs on a small scale is now under way in several clinics. A suggested schedule for procaine penicillin is 150,000 to 300,000 units every day for 10 to 14 days.

Satisfactory response to penicillin therapy of children with congenital syphilis appears to be closely related to the age of the patient at the time treatment is begun. In a group of living children with congenital syphilis studied at the Institute for the Study of Venereal Disease, University of Pennsylvania,[7] it was found that cures approaching 100% were achieved with penicillin when treatment was begun before the third month of life.

If a physician elects to delay treatment, it will be on the assumption that his chances for observing the child for a minimum period of four months are very good indeed. Properly, this observation should include a physical examination and a quantitative serologic test of the child at bi-weekly or monthly intervals, and roentgenograms of the long bones between the fourth and sixth week when possible. Healthy infants born of mothers with positive serologic tests may show a transient positivity, but the passively transferred reagin will decline steadily and will disappear from the noninfected infant's blood within four months after birth. A completely negative examination at the age of 4 months is considered a guarantee that the infant has escaped congenital syphilis.

If on the other hand the presence of infection is established in the infant on the basis of persistently positive serologic tests and confirmatory physical signs, treatment should be started at once in accordance with the schedules discussed above.

5. Even if the mother has been treated for syphilis either before pregnancy or early in pregnancy, the infant's blood should be tested for syphilis at birth. If the test is positive,

even though this does not necessarily indicate congenital syphilis, the doctor's decision to give protective penicillin therapy should depend as before on whether he will be able to observe the baby for at least four months. If the test is negative, and if the mother's syphilitic status is quiescent, there is little or no likelihood that congenital syphilis will develop.

If all these steps were followed, there would presumably be no problem of congenital syphilis in children who have passed early infancy. However, we have a backlog of cases in which the necessary procedures have not been followed. Some of these are children whose mothers have not had serologic tests during pregnancy or at delivery. Others are the children who have not had a blood test or treatment in the neonatal period, although their mothers were known to be syphilitic. The facts about the testing of the mother and baby should be ascertained the first time the baby is seen by the physician in his private practice, well child clinic, or hospital outpatient department, or by the public health nurse in her contact with the family. If the facts indicate the possibility of syphilis, the child should have a blood test at once. Treatment will depend on confirmation of the blood test. The recommended treatment schedules for children under 2 years of age are those previously described, i.e., aqueous penicillin 100,000 u./kg. body weight in divided doses, or, if procaine penicillin is used, 150,000 to 300,000 u./day for 10 to 14 continuous days. For older children, the treatment schedule is the same as for adults.

The question has frequently been raised as to whether a routine serologic test should be given to all school children. This would probably be unproductive, if attempted on a national scale. However, in some areas of relatively high prevalence of syphilis in the general population, mass testing of children under 15 years of age has found roughly 3 to 13% positive or doubtful reactions among Negro children and about 1 to 4% among white children.[8] These data would seem to warrant mass testing of the blood of school children in areas of high prevalence. It would be desirable and practical, if such testing were part of a more inclusive health screening procedure that would include tests for other conditions such as visual and hearing defects, anemia, and other physical handicaps among children of school age.

Of course, when syphilis is discovered in a mother or in one of her children, her other children and the father should be investigated.

SUMMARY

Congenital syphilis still occurs too frequently. The transmission of the disease to infants can be eliminated through adequate case-finding and treatment of pregnant women. For those children who, in spite of past and present efforts to control syphilis among pregnant women, have congenital syphilis, the goal is detection and treatment at the youngest age possible.

BETTY HUSE, M.D., *Pediatric Specialist, Program Planning Branch, Division of Health Services, Children's Bureau*

W. H. AUFRANC, M.D., *Medical Director, Assistant Chief, Division of Venereal Disease, Public Health Service*

MARY S. GOODWIN, M.D., *Special Consultant to Division of Venereal Disease, Public Health Service*

Washington, D.C.

REFERENCES

1. Public Health Service, Federal Security Agency, VD fact sheet, Division of Venereal Disease, Office of Statistics, December 1949.
2. Public Health Service, Federal Security Agency, Congenital syphilis fact sheet, Division of Venereal Disease, Office of Statistics, May 1950.
3. Huse, Betty, and Aufranc, W. H., Proposal for joint action against congenital syphilis, J. Ven. Dis. Inform. **31**:174, 1950; Child **14**:182 and 197, 1950.
4. Heyman, A., and McCain, J. R., Syphilis in pregnancy, New England J. Med. **241**:960, 1949.
5. Goodwin, Mary S., Status of treatment of syphilitic pregnant women and of children who have congenital syphilis, J. Ven. Dis. Inform. **31**:178, 1950.
6. Hogan, R. B., Filter paper microscopic test for syphilis or FPM, J. Ven. Dis. Inform. **31**:37, 1950.
7. Rose, Elizabeth K., György, P., and Ingraham, N. R., Jr., Treatment of infantile congenital syphilis, Am. J. Dis. Child. **77**:720, 1950.
8. Public Health Service, Federal Security Agency, unpublished data, Venereal Disease Division.

NEWS AND ANNOUNCEMENTS

The Harvard Medical School announces an intensive graduate course in Pediatric Endocrinology and Metabolic Disease, Oct. 2 to 7, 1950, 9:00 A.M. to 4:30 P.M. daily, by Dr. N. B. Talbot and Staff, Children's Medical Service, Massachusetts General Hospital, Boston. For details, write: Courses for Graduates, Harvard Medical School, Boston.

ERRATUM

Spragins, M., Shinners, B. M., and Rochester, Betsey, Measles encephalitis: Clinical and electroencephalographic study, PEDIATRICS 5:599, 1950. The word "rubella" should be transposed to "rubeola" (measles) throughout.

Wilson, J. G., and Warkany, J., Cardiac and aortic arch anomalies in offspring of vitamin A deficient rats correlated with similar human anomalies, PEDIATRICS 5:708, 1950. Figures 7 (p. 717) and 10 (p. 722) are reproduced correctly below and on the following page.

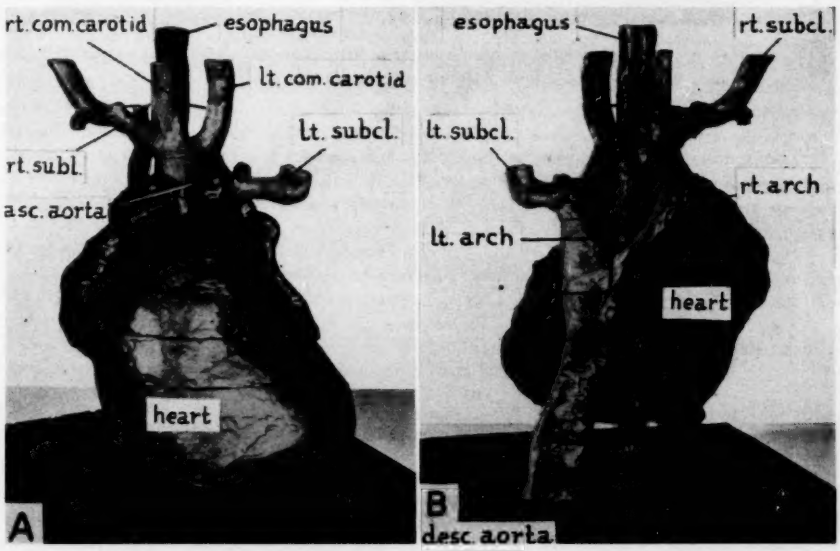

FIG. 7. Wax reconstruction model of heart and major arteries in rat with double aortic arch. A. Anterior view. B. Posterior view.

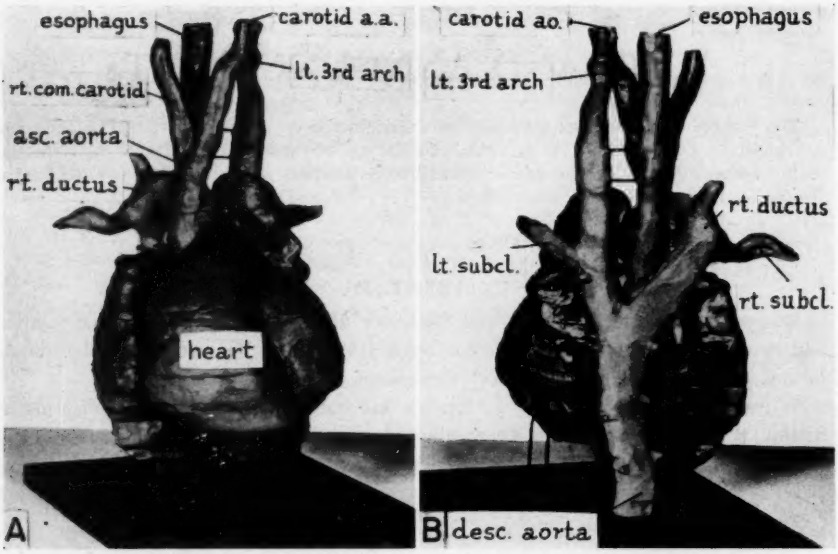

FIG. 10. Wax reconstruction model of heart and major arteries in rat with arterial pattern shown in Fig. 9A. A. Anterior view. B. Posterior view.

* * *

The senior author's address is James G. Wilson, Ph.D., Department of Anatomy, University of Rochester, Rochester, N.Y.

BOOK REVIEWS

PSYCHOLOGICAL PROBLEMS IN MENTAL DEFICIENCY, Seymour B. Sarason, Ph.D., New York, Harper & Brothers, 1949, $5.00, 366 pp.

Here is a book on problems in mental deficiency which is long overdue. It provides a well written, authoritative discussion of diagnostic criteria and classification, and a critical evaluation of current psychologic theories and practices in this field. It has the virtue of clarifying one's thinking about mental deficiency and of making one's approach to the problem sounder and more practical.

This reviewer feels that the pediatrician, along with other workers who deal with mentally defective children, will find this a tremendously valuable book. The discussions of problems of test interpretation criteria for diagnosis and the effect of cultural factors are particularly timely and illuminating. If Dr. Sarason would add a few more words in regard to helping parents of these children and in regard to home-training programs, its value to the practitioner would be further enhanced.

TECHNIQUES OF HISTO- AND CYTOCHEMISTRY, David Glick, Ph.D., New York, Interscience Publishers, 1949, $8.00, 507 pp.

This useful book is a manual of morphologic and quantitative micro-methods for inorganic, organic and enzyme constituents in biologic materials. It is divided into 4 parts: microscopical technics, chemical technics, microbiologic technics and mechanical separation of cellular components. The opening section on microscopical technics differs from standard references on histologic methods: The portion on fixation and imbedding is devoted to a modification of the Altman-Gersh freezing drying technic. The remainder of this part of the book deals with methods aimed at visualizing various inorganic, organic and enzyme constituents of tissues by known chemical and physical procedures. As might be expected, not all the methods are equally precise or specific. The author makes some effort to orient the reader with respect to the chemical basis of various procedures and in some places indicates the shortcomings of the methods.

The largest section is that devoted to chemical technics. Those dealt with are all micro-methods and include various means of measuring respiration, microcolorimetry, microtitrimetry and specific gravity. This section is potentially useful since it brings together under 1 cover the details of many procedures which are otherwise widely scattered in the literature.

The portion on microbiologic technics is extremely brief and not very useful. The section on mechanical separation of cellular components offers a good starting point for those interested in these problems.

Despite some of its shortcomings this book is a worth while addition to the working library of anyone interested in the chemical investigative aspects of medicine.

PATHOLOGY, W. A. D. Anderson, M.D., St. Louis, C. V. Mosby Company, 1948, $15.00, 1453 pp.

An excellent reference volume or textbook on pathology has been compiled by the editor with the assistance of 31 collaborators who prepared 46 chapters supported by nearly 1200 illustrations including 10 full page color plates. Introductory chapters include the subjects of behavior of cells and inflammation. Another section on general principles deals with infection and resistance. Metabolic disturbances which concern fat, carbohydrate, protein, minerals and pigments are considered in a fine discussion by the editor. Problems on circulation, e.g., edema, hemorrhage, shock and thrombosis, are dealt with in a separate chapter. Careful presentation is given to the mechanisms and resulting tissue changes due to physical agents: mechanical, atmospheric, heat, cold, sound and electric. One chapter of special interest to the pediatrician is that on chemical injury in which is included anesthetic deaths. In keeping with the age, there is a discussion on the effects of radiation in which observations on the embryo as well as the effects of atomic bomb injuries are included. Tuberculosis is considered in the usual manner with but brief mention of the features which relate to children. Under spirochetal and venereal diseases, the subject of congenital syphilis received some attention. An excellent discussion of rickettsial and viral diseases is given together with adequate attention to fungal,

protozoal and helminthic infections. The pediatrician will find the chapter devoted to vitamins and deficiency diseases useful but not comprehensive. However, in later chapters dealing with osseous diseases, details are given regarding rickets and scurvy. No especial attention is given the problem of neoplasms of the childhood period. Excellently prepared chapters are those on the heart, blood vessels, kidneys, in fact the presentations on all the organs and systems are well organized. The ductless glands are dealt with in considerable detail in individual chapters, most of which were written by the editor. The disorders of the skin comprise a rather long chapter of 62 pages including on the average somewhat more than 1 illustration to the page. The bones and joints each have a separate chapter and there is 1 on heredity and constitution in disease. None of the contributors appears to be associated exclusively with children's hospitals although the titles of 2 mention among their appointments children's and women's and children's hospitals. The physician who is interested primarily in diseases of children is aware of the lack of sections on deaths peculiar to the neonatal period, the first year of life, prematurity, as well as summary statements pertinent to the various problems as they concern children. There is no doubt that this volume is a fine source or reference book not only for the practicing physician but for the general pathologist as well. The uniformly clear and abundant illustrations of both gross and microscopic features add greatly to the effectiveness of the volume. The references are conveniently arranged at the end of each chapter.